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National Foundation Conference on Rheumatoid Arthritis

INTRODUCTION TO NATIONAL FOUNDATION CONFERENCE ON RHEUMATOID ARTHRITIS

THE following papers were presented at a conference held on April 4, 1959, under the auspices of The National Foundation (originally the National Foundation for Infantile Paralysis).

In the summer of 1958, The National Foundation, which for more than 20 years had supported extensive research in the field of poliomyelitis, announced that it was broadening its program to include congenital malformations and arthritis. Accordingly, two conferences were held, one on rheumatoid arthritis and one on congenital malformations, in order that The National Foundation's medical advisory committees might hear a review of what has already been accomplished in these fields and what needs to be done. The papers on congenital malformations appeared in a previous issue.*

Rheumatoid arthritis presents few opportunities for precise clinical and laboratory measurements. Cumulative knowledge of this disease is descriptive in nature and, as yet, provides no clues which show real promise of leading to discovery of its causation. As with other diseases which have finally yielded to research, a prevention or cure will evolve from the efforts of many scientists, exploring many avenues of inquiry.

The first paper recounts progress in research into the nature of rheumatoid disease and the development of current clinical concepts and methods of treatment. Other papers summarize knowledge of basic anatomic changes and the

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serologic abnormalities which have more recently become identified with this disease. The results of investigations of the chemistry and physiology of fibrous connective tissue are described. And finally some attractive approaches to the problem of pathogenesis are presented, including the possible role of hypersensitivity.

I wish to express the gratitude of The National Foundation to the participants of this conference. Their labors in weaving together so many fragments of seemingly related knowledge are to be commended.

WILLIAM S. CLARK, M.D.
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VOL.
10
1959

RHEUMATOID ARTHRITIS: HISTORICAL ASPECTS

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THE year 1959 marks the one hundredth anniversary of the introduction of the term "rheumatoid arthritis" into medical literature. Sir Alfred Baring Garrod, physician to the West London Hospital, coined this name in 1859, wishing, as he stated, "to imply an inflammatory affection of the joints, not unlike rheumatism in some of its characters, but differing materially from it."[1] At that time rheumatism was the common designation for rheumatic fever; the term rheumatoid arthritis thus may be freely translated as joint inflammation resembling that seen in rheumatic fever. Perhaps such a vague term is fitting for our subject since it contains no etiological implications nor does it attempt to be descriptive of a condition which may assume an infinite variety of forms. In this country, the name "rheumatoid arthritis" was not adopted by the American Rheumatism Association until 1941, when it took the place of at least two synonyms, atrophic arthritis and chronic infectious arthritis. Thus, today, the term "rheumatoid arthritis" is in general use throughout the English-speaking world and in Scandinavia, while the Germans still prefer "primary chronic polyarthritis" and the French "la polyarthrite chronique évolutive." An international committee has recently completed the Herculean task of preparing a classification of joint disease for universal adoption. Until their results are available, I will continue to refer to the simple, if unmeaningful, term "rheumatoid arthritis."

Of greater interest, perhaps, is the antiquity of the disease. In the Hippocratic writings, the word "arthritis" appears but clinical descriptions are given only of podagra or gout and of rheumatic fever. Aretaeus, who lived in the first century A.D., gave a good account of a condition resembling rheumatoid arthritis, describing the onset in small joints with spread to others, as well as the

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systemic changes and deformities.[2] He also stated that the true causes of arthritis were known only to the gods. Anatomic evidence of the existence of rheumatoid arthritis is available in skeletons unearthed in Egypt and dating back to the same period.[3] Although the disease undoubtedly was prevalent in the middle ages, because of influence of Galen, all generalized joint affections were lumped together under the term "arthritis." The first explicit description of rheumatoid arthritis in the modern era was by Thomas Sydenham in 1683.[4] We may conclude then that the disease is not one of recent origin and, of some epidemiologic import, did not arise because of any relatively recent change in man's environment or manner of living.

DEVELOPMENT AS DISEASE ENTITY

I should next like to trace briefly the steps by which rheumatoid arthritis has gradually become accepted, in the opinion of most, as a disease entity. The process has been an interesting one and has been made up of two interwoven phases. The first might be termed "analysis," or the setting off of what seemed distinct diseases from a heterogeneous group, and the second, "synthesis," or the bringing together of conditions regarded merely as clinical or pathologic variants of one disease. Even today there is no common agreement as to what conditions should be included under or excluded from our concept of rheumatoid arthritis. Diagnostic criteria have thus inevitably prefaced clinical or laboratory studies of this disease, although it is hoped that those recently developed by a committee of the American Rheumatism Association[5] will prove useful as a common reference point until a specific diagnostic test is available or until more complete knowledge is attained of the etiology and pathogenesis of the disease.

Analytic Process (Table I).—The late seventeenth century saw the first clear distinction between gout and both acute and chronic rheumatism. From this time on, the identity of gout was gradually established, aided immeasurably by the discovery in 1848 by the same Garrod who gave us the name "rheumatoid arthritis" that the excess of uric acid in the blood, so typical of gout, is absent

TABLE I. CONDITIONS SET OFF FROM RHEUMATOID ARTHRITIS

Gout
Osteoarthritis (degenerative joint disease)
Rheumatic fever
Infectious arthritis
Tuberculous
Syphilitic
Brucellar
Gonococcal
Connective tissue diseases (other than rheumatoid arthritis and rheumatic fever)
Periarteritis nodosa
Systemic lupus erythematosus
Dermatomyositis
Scleroderma

in rheumatoid arthritis. Today in practically all quarters, gout is sharply separated from rheumatoid arthritis and other forms of joint disease. It is still of practical importance, however, for the clinician to realize that rheumatoid arthritis may occur in early stages in an episodic form, mimicking acute gouty attacks. Furthermore, chronic gouty arthritis may resemble rheumatoid arthritis in a chronic progressive stage. In one such case,[6] pathologic studies showed rheumatoid-like synovial proliferation apparently caused by urate deposits. The possibility is thus suggested that the lesions of rheumatoid arthritis may be due to a metabolic disturbance, with the deposition of a chemical substance in the connective tissue concerned.

The other great type of chronic joint disease, osteoarthritis or degenerative joint disease, which we all have to a greater or lesser degree but fortunately usually without obvious symptoms, was not definitely distinguished from rheumatoid arthritis until early in this century. This distinction continues to be generally accepted, with the realization that many older patients demonstrate features of both diseases and that joint damage from rheumatoid arthritis is one of the causes of the secondary type of degenerative joint disease. Another point of confusion which crops up, especially in population surveys, is the occasional appearance in degenerative joint disease of synovial and periarticular inflammation.[7]

Over 250 years ago, Sydenham[4] set off acute rheumatism, meaning rheumatic fever, from chronic forms of arthritis. In spite of the antiquity of this distinction, the identity of rheumatic fever and rheumatoid arthritis has continued to be maintained by some on clinical as well as pathologic grounds. The German name for rheumatoid arthritis, primary chronic polyarthritis, is used to distinguish it from the so-called secondary form, which supposedly arises as a sequel to rheumatic fever and contains a high proportion of patients with valvular heart disease. In England and the United States, the opposite view has predominated. That rheumatoid arthritis may arise in an acute "atypical" form which simulates rheumatic fever is recognized as is the fact that patients who actually have rheumatic fever may present for a time some of the articular features of rheumatoid arthritis. Another possibility is the occasional coincidence of the two diseases in the same individual—the most common sequence being the development of rheumatic heart disease secondary to rheumatic fever in childhood, followed at an appreciable interval by the onset of unmistakable rheumatoid arthritis.[8] A follow-up study in this country of a large series of patients with rheumatic fever indicates that such a combination occurs infrequently, perhaps not more often than might be expected by chance.[8]

More difficult to explain are the postmortem findings at autopsy of what is apparently rheumatic heart disease with gross valvular deformities in a high proportion of patients with typical severe rheumatoid arthritis.[9,10] Such cases can be distinguished from those with what might be termed rheumatoid heart disease, which may occur in two forms. In the first, granulomatous lesions similar to those found in the rheumatoid subcutaneous nodules have produced valve deformities,[11] and, in the second, aortitis and aortic insufficiency have been recognized as manifestations of what may be the spinal form of rheumatoid

arthritis,[12] one of the variants which I shall consider later. These two forms, however, probably account for only a small part of the cardiac lesions (exclusive of pericarditis) found in rheumatoid arthritis. Perhaps Dr. Kulka will allude to the possibility that healed or minor lesions of the first type may lead to deformities indistinguishable from those of rheumatic heart disease. Space does not permit further consideration of the clinical and pathologic relationships of the two diseases. For the present, the differences seem so marked that, in the absence of etiological evidence to the contrary, the two conditions should be looked on as separate entities. Nevertheless those of us concerned with clinical and laboratory investigation in rheumatoid arthritis must continue to be open-minded and alive to developments in rheumatic fever, a disease generally believed to occur as a delayed sequel of infections with Group A hemolytic streptococci.

In the evolution of rheumatoid arthritis as an independent disease, the growth of clinical bacteriology made possible the setting off of diseases of the joints due to specific infections. Such separation is easy and obvious in some patients; in others the distinction becomes difficult and uncertain. For example, acute forms of rheumatoid arthritis involving one or a few large joints may mimic almost exactly arthritis due to a specific infection. Where a bacteriologic or serologic diagnosis is apparently made, the question arises as to whether or not the patient has an infectious disease in addition to rheumatoid arthritis, or even if microorganisms are recovered from synovial fluid or articular tissue, whether or not two independent diseases of the joints may be present. Finally, some evidence has been presented that a condition resembling rheumatoid arthritis in a chronic, progressive form may be caused by any one of a number of microorganisms.

Articular manifestations have been noted in over 30 diseases of known infectious etiology. These include viral diseases such as rubella and mumps; bacterial diseases; mycotic, for example, coccidioidomycosis; spirochetal (syphilis); protozoal (malaria and trypanosomiasis); and metazoal (filariasis). In most of them, the diagnosis can readily be made and there is little possibility of confusion with rheumatoid arthritis. In patients, in whom a chronic arthritis resembling rheumatoid arthritis in all respects follows an infectious disease, however, the question arises as to whether or not the patient actually has a chronic arthritis of specific infectious origin. Space does not permit more than a brief categorical summary of present evidence in regard to a few common infections.

Tuberculous arthritis may occasionally involve multiple joints (just as rheumatoid may be persistently monarticular), and visceral or articular tuberculosis may occur in a rheumatoid patient. But the concept of a chronic progressive polyarthritis of tuberculous nature, which was postulated by Poncet[13] over 50 years ago and was given the name "tuberculous rheumatism," remains to be established by incontrovertible proof.[14] A similar conclusion may be reached in the case of syphilis, although a bilateral synovitis, usually in the knees, is one of the cardinal manifestations of the congenital form, and there is suggestive evidence that a transitory polyarthritis may occur in the secondary stage of the acquired disease.[15]

While articular symptoms and even synovitis are among the common manifestations of brucellosis, chronic arthritis of the rheumatoid type has been clinically observed in relatively few patients with the diagnosis of this disease. Attempts have been made to implicate brucellar infection as an etiological agent of rheumatoid arthritis, but it is highly probable that such patients really have rheumatoid arthritis along with a past or present brucellar infection.[16]

Since gonorrheal arthritis starts in a polyarticular form more often than in only one joint, the differential diagnosis between it and rheumatoid arthritis with an acute onset is sometimes difficult. The passage of time usually makes the distinction clear. Except for recurrent forms resulting from either reinfection or exacerbation in the genitourinary focus, gonorrheal arthritis may be considered a self-limiting disease, tending toward either complete restitution of the joints or toward varying degrees of scarring or deformity.[17] While rheumatoid arthritis may be precipitated by or aggravated by a gonorrheal infection, such a condition in no sense represents a form of chronic joint disease caused by the gonococcus.[18]

I shall conclude the account of the analytic process by which rheumatoid arthritis became set off from other forms of joint disease by reference to the so-called connective tissue diseases in all of which, incidentally, arthritis may appear during the course. The concept of connective tissue disease was introduced by Klinge[19] about 30 years ago in relation to rheumatic fever. In the last 10 or 15 years, largely through the work of Klemperer,[20] the term "collagen" (or, better, "connective tissue") disease has come to be applied chiefly to periarteritis nodosa, systemic lupus erythematosus, dermatomyositis, and scleroderma, in addition to rheumatic fever and rheumatoid arthritis. On a pathologic basis, these diseases may be grouped together on account of a common attribute, the widespread involvement of connective tissue throughout the body. In most cases, sufficiently characteristic features are found at autopsy to enable the pathologist to distinguish among them on histologic grounds and supply a specific anatomic diagnosis to the clinician. Nevertheless, not infrequently, overlapping features or even typical pathologic features of two or more of these disorders are present in the same patient. Similarly, although the individual connective tissue disorders usually sooner or later conform to distinct disease patterns, clinical manifestations of more than one may appear in the same patient, either simultaneously or in sequence. For these reasons, a relationship among these diseases in regard to etiology or pathogenesis has been postulated, but remains as yet unproved. The possibility of a common etiology should continue to be entertained from an investigative standpoint. But it seems best at present to regard each disease as distinct, with the full understanding that in certain patients it may be impossible to apply a single diagnostic label either at the onset, throughout the course, or even at autopsy.

Synthesis.—I should next like to discuss briefly a few syndromes which are regarded by some as variants of rheumatoid arthritis and by others as independent disease entities (Table II). The first is juvenile rheumatoid arthritis or Still's disease. This eponym arose from a paper given in London in 1896 by Dr. George

F. Still, entitled "On a Form of Chronic Joint Disease in Children."[21] This date marks the origin of the conception that a form of arthritis exists in childhood which makes up a distinct clinical and pathologic entity. Up to this time, as Still himself stated, the identity of the juvenile and adult forms was never questioned. Still did describe certain previously unrecognized features of rheumatoid arthritis in children, but because of the confusion of the times about the classification of the two great types of chronic arthritis he promulgated a distinction which is now generally regarded as unnecessary and misleading. At present it is pretty well agreed that it would be wiser to drop the term Still's disease from our nomenclature and regard juvenile rheumatoid arthritis as a variant of rheumatoid arthritis, which, to be sure, may present clinical and laboratory differences when compared with the adult form.

TABLE II. POSSIBLE VARIANTS OF RHEUMATOID ARTHRITIS

Juvenile rheumatoid arthritis (Still's disease)
Felty's syndrome
Rheumatoid (ankylosing) spondylitis
"Psoriatic arthritis"
Arthritis of ulcerative colitis
Intermittent hydrarthrosis
Palindromic rheumatism

Since I understand that The National Foundation is especially interested in children with rheumatoid arthritis, it might be useful to list briefly some of these differences. In the first place, the disease in children must still be regarded as relatively rare and as necessarily making up only a small portion of any large series of patients of all ages with rheumatoid arthritis. In one clinic it was found that the disease began at the age of 12 or younger in only 5 per cent of about 1,100 patients with rheumatoid arthritis seen over a period of 18 years.[22] No possible cause for this low frequency has yet been established although it may be noted in passing that such age distribution is exceptional in diseases known to be of infectious origin. Other differences include a greater tendency toward: (1) a high degree of fever, often out of proportion to the arthritis, (2) initial involvement of large joints, (3) pleurisy and pericarditis, (4) enlargement of spleen, lymph nodes, and liver, (5) eye involvement with so-called band keratitis, (6) growth disturbances, and (7) a characteristic rash.

Two final points of difference are a lower frequency of subcutaneous nodules and, perhaps in keeping with the first, a much lower frequency of positive serologic tests, unless measurement is made of the agglutinating or inhibiting activity of the euglobulin fraction. The clinical course and prognosis for life and freedom from major disability in juvenile rheumatoid arthritis is probably roughly similar to those in the adult form, in spite of the gloomy impression given by one report from a chronic disease hospital dealing with a preponderance of severe cases.[23]

Since enlargement of the lymph nodes and spleen may occur also in adults with rheumatoid arthritis, we run into two additional eponyms, Still-Chauffard

syndrome and Felty's syndrome. The former is used chiefly in Europe but the latter originated at The Johns Hopkins Hospital in 1924 when Felty described 5 cases of chronic arthritis and splenomegaly and leukopenia in adults.[24] Since rheumatoid arthritis is a generalized disease that may affect with varying frequency the lymph nodes, spleen, bone marrow, and many other tissues besides the joints, perpetuation of these syndromes seems undesirable. It is of interest, however, that 4 of Dr. Kunkel's 7 patients with "uniquely large amounts of rheumatoid factor" had splenomegaly and leukopenia and thus qualified for the diagnosis of Felty's syndrome.[25]

Opinion is still divided as to whether what is called rheumatoid spondylitis in this country and ankylosing spondylitis abroad should be considered a form of rheumatoid arthritis which chiefly affects the spine or a disease sui generis. Patients with this condition in an advanced form present a distinctive clinical and radiologic picture, which would doubtlessly be regarded as an independent entity but for one fact: many of these patients have peripheral joint involvement indistinguishable from that seen in rheumatoid arthritis and including at times the small joints of the hands and feet. Pathologic examination of these joints, as well as of the diarthrodial joints of the spine, shows changes consistent with a diagnosis of rheumatoid arthritis.[26] Space permits a recounting of only a few details of this rather controversial subject. Those who favor a separate entity status for this condition point out its preponderantly male sex distribution compared to the excess of females with peripheral rheumatoid arthritis, an earlier age of onset, an increased frequency of uveitis, and the failure to find subcutaneous nodules in patients without peripheral arthritis in addition to involvement of the spine. The strongest argument brought forth in recent years is the almost consistent failure to demonstrate the so-called rheumatoid factor in these patients by most of the available serologic tests. In the absence of further knowledge, the classification of this form of spinal arthritis must remain a matter of opinion. As far as the reversal of the sex ratio is concerned, a similar situation is present in diseases of known etiology. For example, syphilis involving the cardiovascular and nervous systems shows a predilection for males out of all proportion to the nearly equal sex distribution of the disease as a whole.[27]

That there is a relationship between psoriasis and rheumatoid arthritis has been noted for nearly 100 years, chiefly because of the frequency with which this skin disease occurs among patients with the clinical features of rheumatoid arthritis. As in the case of spondylitis, opinion is far from unanimous in regard to whether there is merely an interesting association between the two diseases or whether a separate entity should be recognized and designated arthropathia psoriatica or, more simply, psoriatic arthritis. Again, those who believe the combination to be a separate entity have received material support from the almost uniformly negative results of most serologic tests for rheumatoid arthritis in these patients. Clinical and histopathologic evidence, however, still favors an association of two diseases, with the features of the one often modified by the presence of the other. There is perhaps one exception in the patient who has arthritis of the terminal interphalangeal joints in close association with psoriasis

of the corresponding nails.[28] The question, of course, cannot be solved in the present state of our knowledge of the etiopathology of the two. In the meantime, all of us dealing with rheumatoid arthritis must remain alive to developments in the study of psoriasis, since important clues to the nature of rheumatoid arthritis may arise in the course of investigation of this common and still mysterious skin disorder.

Arthritis is stated to be the most common extraintestinal complication of idiopathic chronic ulcerative colitis, in a frequency ranging from 4 to 8 per cent of the cases in various series. The exact nature of this relationship is still undetermined. In many of the patients, the arthritis is chronic and progressive and resembles rheumatoid arthritis clinically and in the type of synovitis found in biopsy and autopsy material. In others, the arthritis is episodic and corresponds in appearance and recovery to exacerbations and remissions in the colitis.[29] The latter type may also be accompanied by erythema nodosum. Once more, opinion is divided in regard to the classification of this form of joint disease. It is possible but certainly not yet established that both opinions are correct, that is, that certain cases represent a systemic manifestation of the colitis, while others make up an interesting association between two disabling diseases of unknown etiology.

VOL. 10 1959

The last two possible variants of rheumatoid arthritis are rather rare conditions, which I shall mention briefly. Intermittent hydrarthrosis, first described in 1845,[30] is one of the group of maladies classified by Reimann[31] under the heading of "periodic disease." It is marked by joint swelling (usually of the knee) occurring at regular intervals with mathematical precision. One of our patients, who was an enthusiastic angler, timed her fishing trips to correspond with the interval of about 2 weeks between attacks. The chief reason for regarding this condition as a variant of rheumatoid arthritis is that most such patients, if followed long enough, will eventually develop chronic joint disease consistent with rheumatoid arthritis. In others, intermittent hydrarthrosis may appear as a manifestation of an established arthritis of the rheumatoid type.

Nearly 100 years after the first description of intermittent hydrarthrosis, Philip Hench identified the last syndrome in our list and gave it the name palindromic or recurrent rheumatism.[32] Briefly, the condition consists in transitory articular or para-articular swelling lasting a few hours or a day or so and reappearing at frequent but irregular intervals. The present status of palindromic rheumatism in relation to rheumatoid arthritis is analogous to that of intermittent hydrarthrosis since, in a number of cases, this syndrome has been the first manifestation of or the accompaniment of chronic rheumatoid arthritis.

DESCRIPTION OF THE DISEASE

The preceding section has been devoted to a necessarily brief and perhaps oversimplified account of the development of the concept of rheumatoid arthritis as a disease entity. In the course of this attempt, I am sure that you have become aware that in not a few respects the boundaries of this disease cannot be

accurately delineated with our present knowledge. In such instances, the student of rheumatoid arthritis must adopt temporary criteria, which he realizes may be later overruled. As expressed by the late Justice Holmes, "An opinion yields later to the impact of facts unforeseen."[33]

It has not been my intention to leave the impression that the diagnosis of rheumatoid arthritis is made chiefly by exclusion. On the contrary, when this disease has reached a well-developed stage, it presents an unmistakable appearance, so that, with rare exceptions, the diagnosis can be made with reasonable certainty at a glance. As I shall next outline, a patient with established rheumatoid arthritis can be identified by characteristic symptoms, physical signs, articular roentgenograms, and histopathologic findings, at least in the subcutaneous nodule and synovial membrane. Proof of the identity of rheumatoid arthritis on etiological grounds is, of course, still lacking. However, studies in recent years suggest that a serologic test of diagnostic significance may before long be available—that is, one with an adequate combination of sensitivity and specificity.

It is customary to start a description of a disease with a definition, preferably in one sentence. One that we have employed reads as follows: "Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology and pathogenesis which is systemic in nature and characterized by the manner in which it involves joints." It is also a familial disease in that it occurs more frequently in the relatives of patients than of controls. Of some interest, in view of the relationship often postulated between rheumatoid arthritis and rheumatic fever, is a similar difference with respect to a family history of rheumatic fever (Table III). Although the familial nature of rheumatoid arthritis is generally admitted, no conclusions can yet be drawn as to the relative influence of environment, contagion, or heredity. If the last plays an important part, no generally accepted genetic mechanism has as yet been proposed. Females are more commonly affected, in a ratio of at least 2 to 1, except that the reverse is true in the possible variant, rheumatoid or ankylosing spondylitis. A preponderance of females is found in all age groups, including children, and as yet remains unexplained. The onset of the disease may occur at any age, although apparently less commonly in childhood. The available data, drawn from hospital or clinic rather than population studies, also suggest that there is an increased incidence in women at and following the usual time of menopause.[34]

TABLE III. FREQUENCY OF RHEUMATIC DISEASE IN FAMILIES OF 293 PATIENTS WITH RHEUMATOID ARTHRITIS COMPARED WITH THOSE OF 293 CONTROLS

TYPE OF DISEASE	PATIENTS (%)	CONTROLS (%)	DIFFERENCE IN PERCENTAGES (± S.E. OF DIFFERENCE)
Rheumatoid arthritis	11.9	5.1	6.8 ± 2.3
Rheumatic fever	11.6	3.1	8.5 ± 2.1
Undetermined and other forms of rheumatism	23.2	12.6	10.6 ± 3.1

From the earliest descriptions of rheumatoid arthritis, it has been noted that symptoms not necessarily related to the joints may precede the actual development of arthritis. The most common of these are fatigue, anorexia, weight loss, musculoskeletal pains, sensory disturbances of the extremities, and vasomotor instability. A prodromal stage may thus be arbitrarily set off if desired, with the proviso that symptoms of this type may actually mark the beginning of the disease. (In some instances, however, they may date back to many years before the appearance of a definite arthritis and thus perhaps rather represent a constitutional background favorable to its development.) Various potentially disturbing events may precede the onset of arthritis, most commonly mental or physical strain and infections; exposure to cold or dampness, surgical operation or trauma less frequently are noted as so-called precipitating factors (Table IV). If we accept the premise that the prodromal period may mark the real beginning of the disease, then the precipitants seem usually to determine a more disabling phase with articular localization of the morbid process. Or, as put more vividly by Fuller[35] nearly 100 years ago ". . . when the rheumatic poison is present in the system, any disturbing circumstance . . . such as overfatigue, anxiety, grief, or anger . . . may prove the accidental or exciting cause of the disease. . . ."

VOL. 10 1959

TABLE IV. PRECIPITATING FACTORS IN 293 PATIENTS WITH RHEUMATOID ARTHRITIS

FACTOR	PATIENTS	
	NUMBER	PER CENT
Strain	80	27.3
Infection	49	16.7
Exposure	31	10.6
Operation	16	5.5
Trauma	15	5.1

The type of onset in rheumatoid arthritis ranges from the explosive to the insidious, with endless variations in between. As mentioned before, the initial attack may simulate rheumatic fever or a specific infectious arthritis, or the process may come on gradually and remain mild for many years. Large or small joints may be initially involved, in about equal frequency, with joints of the legs first affected at least as commonly as those of the upper extremities. The joints may be affected at first in a migratory or episodic fashion but later usually with unrelenting persistence. Symptoms noted in the prodromal period, such as fatigue, anorexia, and weight loss usually persist or become more marked. Vasomotor instability, including cold hands and feet, paresthesias, cyanosis, and "vascular spasm" resembling Raynaud's disease are frequent accompaniments, while muscle weakness, tremor, radiating pains, and hyperactive tendon reflexes suggest primary or secondary involvement of the nervous system. I shall allude later to the vasomotor and neurologic manifestations.

Physical examination of the joints reveals no early changes specifically differing from other forms of arthritis. Periarticular inflammation, often with effusion, usually precedes the development of limitation of motion or deformity. The latter includes subluxation, most often of knees, wrists, and metacarpal phalangeal joints and ulnar deviation of the fingers, and may present a characteristic appearance, especially in the hands. Although involvement of one or a few joints is not uncommon in early stages, the arthritis usually eventually assumes a symmetrical polyarticular distribution. I might add that although the first description of symmetrical joint involvement in rheumatoid arthritis appeared in 1836,[36] a plausible explanation of the reason for or mechanism of this distribution is yet to appear. Muscular atrophy is a prominent part of the disease picture, evidently not due solely to disuse since the atrophy may appear before the development of arthritis or in relation to joints still maintaining full function. Involvement of tendons, bursae, and fasciae is also frequently present. Subcutaneous nodules form a characteristic part of the picture in about 20 per cent of cases observed over a long period. The elbow represents the most common site for nodule formation and it is generally believed that irritation and minor trauma, particularly over bony prominences, may often constitute the determining factor in nodule location. However, nodules similar in histologic appearance to those found in the subcutaneous tissues have been identified in the sclera, pericardium, heart valves, pleura, lungs, and synovial membrane.

Fever and tachycardia are common findings, which testify to the systemic nature of the disease. Involvement of nonarticular tissues and of other organs of the body is evidenced in many cases. In the skin, pigmentation and atrophy may appear, and characteristic rashes are seen especially in the juvenile form. Lymphadenopathy is a common finding and splenomegaly is present in less than 10 per cent of adults, but more frequently in children.[34] I have already referred to cardiac involvement, most common clinically in the form of pericarditis. No characteristic changes have been described in the kidneys or central nervous system but pleurisy is a definite manifestation and there is evidence that the disease may involve the lung. Focal inflammatory lesions of a nonspecific nature are commonly found in pathologic examination of muscles and peripheral nerves. Ocular changes, including uveitis, keratitis, and scleritis, may constitute disabling manifestations and even lead to blindness.

On the laboratory side, anemia is commonly found, the mechanism of which is not yet fully elucidated. Variations in the white blood cell picture are not diagnostic with higher counts found in acute cases, especially in children, and normal or low white cell counts in patients with more advanced disease. An interesting and unexplained finding is that of eosinophilia in about 10 per cent, occasionally of a high degree. Amyloidosis is found at autopsy in 25 per cent of long-standing cases in the absence of other causes such as tuberculosis or intercurrent infection. Systematic examination of the synovial fluid does not yield specific diagnostic criteria for rheumatoid arthritis but may be helpful in ruling out traumatic arthritis and osteoarthritis with articular effusions, as well as arthritis with a purulent type of effusion due to a specific infection. Other-

wise, chemical and cytologic features of the synovial fluid in rheumatoid arthritis may often be duplicated in various forms of joint disease, including gouty arthritis and rheumatic fever.[37] Although significantly low basal metabolism rates have been found in rheumatoid patients for more than 30 years, only recently has a true hypothyroidism been demonstrated.[38] This finding assumes additional interest since the demonstration of thyroglobulin antibodies in thyroid disease.[39]

In 1703, long before the advent of clinical laboratory methods, the "buffy clot," which we now know represented the increased sedimentation rate of the red blood cells, was observed by Musgrave[40] in rheumatoid arthritis. Over 200 years later, in 1924, the first extensive investigation of the sedimentation rate in arthritis was made by Herrman.[41] In a sense, this work may be regarded as the start of serologic diagnosis in rheumatoid arthritis. The sedimentation rate is of course entirely a nonspecific reaction and is increased in most infectious diseases as well as in malignant growths and in pregnancy. The exact mechanism of this reaction is not known but is believed to be associated with alterations in the plasma proteins, with increase in fibrinogen the most common factor. This test remains a useful diagnostic tool and a rough measure of rheumatoid activity, although it may be normal in early cases and in those with inactive disease.

In 1930, Cecil, Nicholls, and Stainsby,[42] as part of an attempt to establish the streptococcal etiology of rheumatoid arthritis, observed that the hemolytic streptococci supposedly recovered from the blood and synovial fluid of patients with this disease were uniformly agglutinated to a high titer in rheumatoid sera. It was later found that similar reactions were given by streptococci from other sources and by R forms of the pneumococcus. It is now clear that the phenomenon of bacterial agglutination in rheumatoid arthritis is nonspecific in regard to the organism involved. I expect that Dr. Kunkel will have something to say in regard to the relationship between this phenomenon and the other agglutinating properties of rheumatoid sera. At any rate, the test is of limited practical value because of its relatively low sensitivity.

The subsequent history of the development of what is now termed the rheumatoid factor I will leave to Dr. Kunkel. I am sure that he will tell you of the observations of Waaler[43] in 1940 and of Rose and Ragan[44] in 1948 in regard to the property of rheumatoid sera of enhancing the agglutination of sensitized sheep red cells and of Wallis[45] in 1946, who found that collodion particles of roughly streptococcal size could be agglutinated by the sera of some rheumatoid patients. Further experience is required with the now numerous tests which utilize the agglutinating property of rheumatoid sera before their diagnostic significance can be finally evaluated. It can at least be said that such advances have enhanced the concept of rheumatoid arthritis as a disease entity.

I have already mentioned that rheumatoid arthritis is a disease of characteristic morbid anatomy. This statement can thus far be applied only to large lymphoid follicles in synovial tissue and to the fully developed rheumatoid nodule. I am sure that Dr. Kulka will show you examples of these lesions, which lend substantial support to the concept that rheumatoid arthritis is a disease entity.

VOL
10
195

In certain diseases, a favorable response to a particular form of therapy constitutes a diagnostic point of great importance—for example, the response of scurvy to ascorbic acid and of acute gouty arthritis to colchicine. As I shall point out later, no curative treatment is yet available for rheumatoid arthritis, while the suppressive action of cortisone and other steroids applies equally to many other diseases. In addition, the ameliorating effect of pregnancy and jaundice is not limited to rheumatoid arthritis.

In view of what I have outlined, is it reasonable to consider rheumatoid arthritis a distinct disease entity? It is entirely possible, of course, that it represents only one type of response to a single agent or disease mechanism which is shared by other disorders. One may equally speculate that multiple causes or mechanisms are responsible for the varied and at times seemingly unrelated clinical pictures included under a single diagnostic heading. A definitive answer to this question can hardly be given until the etiology or pathogenesis has been discovered. Nevertheless, from the considerations mentioned, the weight of medical opinion favors an independent status of this disease, although, as you have heard, certain of its boundaries are still in dispute.

OL.
10
959

NATURAL HISTORY

Space permits only brief reference to a few aspects of the natural history of rheumatoid arthritis. In regard to geographic distribution, it was stated by Dawson[46] in 1935 that it was essentially a disease of temperate climates. Reliable data to substantiate this opinion, as far as I know, are as yet unavailable. The prevalence of the disease is being increasingly studied, both in this country and in Europe. Thus far, population surveys show substantial agreement concerning a prevalence rate of at least 2 or 3 per cent.[47] These studies refer to patients with symptomatic, clinically diagnosable disease and necessarily do not include those who are in remission from a previous mild attack or who may have chiefly systemic manifestations. The course of the disease has been studied chiefly in series derived from patients who come to a particular clinic. Such groups of patients are, of course, ill-defined selections from the total number of individuals with rheumatoid arthritis in the general population. An infinite variety of courses may be encountered in such patients, so that it is impossible to categorize the courses followed by even a small number without encountering numerous minor exceptions. We attempted once to express the course of rheumatoid arthritis in a single sentence, based on hospital and clinic experience, and will quote it here for what it is worth: "The course of the disease may be summarized as usually one of steady or intermittent progression, although complete or nearly complete remissions may occur at first and certain patients recover without significant disability even after years of active disease."[48]

A few of the possible courses may be listed by way of illustration. One is an intermittent course, with remissions usually longer than relapses. The second is an intermittent course without complete remissions and which may finally settle down to a relatively low level of activity or progress toward disability. Next is a gradually progressive disease, which, if it persists 10 years or more is

unlikely to remit. In another, the patient may have a low level of activity and severity for many years and may correspond to those found in population surveys who never consulted a doctor for their arthritis. (In one British survey,[49] over one-third of the females and one-fifth of the males found to have rheumatoid arthritis had never seen a physician for arthritis.) The next example is that of patients with one severe attack who afterward remain well. Finally, there are the fortunately rare patients who have malignant rheumatoid disease which which progresses rapidly to complete disability and death in spite of all efforts.

About one-fourth of one series of hospitalized patients gave histories of an intermittent course, marked by long remissions, before the disease finally became persistent.[34] Studies on these patients also showed that an attack was much less likely to remit when present for over a year. We are in the main ignorant of the causes of exacerbations and remissions in rheumatoid patients. In certain instances, the same factors that may precipitate the original attack are apparently operative before exacerbations. I refer to mental or physical stress; infections, usually of the upper respiratory tract; surgical operations; childbirth; and, less commonly, trauma and exposure to cold and dampness. I have mentioned that intercurrent jaundice and pregnancy may be associated with remissions. A final point is that rheumatoid arthritis, like rheumatic fever, is a seasonal disease, both in onset, and, if remittent, in exacerbations. For example, in the patients with intermittent course, exacerbations occurred about twice as frequently from November through March as in the warmer months of the year. Available information also shows that March is by far the most frequent month of onset.[34]

CAUSE AND CURE

The remainder of my talk will be devoted to a summary of some of the accomplishments to date in the still elusive search for the cause and cure of rheumatoid arthritis. In regard to clinical and epidemiologic studies, examples of which I have just given, it can justly be said that little of a qualitative nature has been added to the clinical description of the disease during the past 50 years. The distinguishing feature of recent clinical descriptions has been the study of large groups of patients in comparison with suitable control groups in order to evaluate the clinical impressions of the past, unravel the clinical variations, and test hypotheses about possible causative factors.

While such studies are contributing to our understanding of the nature of rheumatoid arthritis and its treatment, they have not provided specific leads concerning either the cause or pathogenesis of the disease or of its cure. This is one reason, but hardly the main one, for what might be termed the fundamental approach. It is rather that a better understanding of disease mechanisms and treatment can result only from a greatly extended knowledge of the tissue chiefly involved. The concept of rheumatoid arthritis as one of the connective tissue diseases, now existent for over 20 years, has led directly to an attempt to characterize this tissue in regard to structure, composition, reactivity, and, especially, physiology, so that, as the normal is defined, we can better interpret

the alteration produced by disease. This approach requires the use of modern analytical methods including those developed by physicists and applied by biologists. I shall leave the further development of this topic to Dr. Dorfman.

Etiology.—I come next to a brief account of the investigations directed toward the elucidation of the etiology and pathogenesis of this disease. Rather than attempt a chronologic survey, I have decided to present the subject by referring briefly to some of the more important etiological theories: (1) neurogenic, (2) vascular, (3)infectious, (4)hypersensitivity, (5)metabolic, (6)endocrine, and (7) psychogenic.

Space does not permit a critical discussion of the evidence in each instance; it is perhaps sufficient to state at the outset that we are still ignorant of either the inciting agent of rheumatoid arthritis or of its pathogenetic mechanism.

I have already mentioned the symptoms and signs of the disease which suggest nervous system involvement. These include muscle weakness, tremor, radiating pains, and hyperactive tendon reflexes along with atrophy of muscle, skin, and bone. At the turn of the last century such findings led to what might be called the neurogenic theory of origin, with the disease termed by one writer a toxic trophoneurosis.[50] Although anterior horn cell changes were described as early as 1894[51] subsequent neuropathologic studies have failed to show specific central nervous system lesions.[52]

Perhaps allied to the neurogenic theory, but involving the autonomic nervous system and its chemical mediators, is the hypothesis that the primary inciting agent in rheumatoid arthritis exerts its influence through functional or anatomic changes in the vascular system. From the earliest clinical descriptions of rheumatoid arthritis to the most recent, symptoms and signs connected with increased vasomotor tone have received prominent mention. Attenuation of blood flow to the limbs has been shown by quantitative methods[53] and the increased tendency toward vasomotor instability in women has even been thought to determine the sex ratio of the disease.[54] Vascular lesions form a well-recognized aspect of the fundamental histopathology of rheumatoid arthritis, and cellular reactions in sympathetic ganglia have also been demonstrated.[52] More recently, studies have been made on abnormalities in the excretion of noradrenalin in rheumatoid subjects[55] and Scherbel[56] has demonstrated a strikingly exaggerated response in rheumatoid subjects to the local injection of serotonin and of medullary adrenal hormones. Another interesting clinical observation has been the development of a form of arthritis in several patients with the malignant carcinoid syndrome, in which a marked increase of serotonin production takes place.[57] I hope that Dr. Kulka will refer to his experimental and pathologic studies in regard to the role of the vascular system in the production of connective tissue lesions.

With the advent of the germ theory of disease and the growth of clinical bacteriology, it was not long before the neurogenic theory was gradually lost sight of in the search for a bacterial causation. A variety or organisms were isolated from rheumatoid body fluids and tissues from 1892 on and claims were made for their etiological specificity, which in due course failed to be confirmed.

Probably the most recent of such efforts was the isolation of hemolytic streptococci from the blood and joints of a high proportion of rheumatoid patients by Cecil[42] in 1930, to be finally retracted 10 years later, with the findings believed due to laboratory contaminants. The case in favor of a microbic origin of rheumatoid arthritis can still hardly be considered closed, although experimental transmission of the disease to human volunteers has proved unsuccessful[58] as have efforts to incriminate pleuropneumonia-like organisms or a virus.[59]

For at least 25 years, the hypothesis has frequently been presented that rheumatoid arthritis and other diseases of connective tissue are due to hypersensitivity. Klinge,[60] Rich,[61] and others have demonstrated that vascular and connective tissue lesions resembling those found in human pathologic material can be produced in animals by the injection of antigenically active proteins. Other theories have presumed that a bacterial antigen is operative in extra-articular sites such as so-called foci of infection or that pleuropneumonia-like organisms constitute a living but invisible antigen in the tissues or even that autogenous tissues are rendered antigenic by bacterial or chemical action. The hypersensitivity hypothesis has received substantial impetus in recent years from the demonstration of the inhibiting action of adrenocortical steroids on immune processes and especially from the possibility that the rheumatoid agglutinating factor is concerned in the pathogenesis of the disease, a subject to be discussed by Dr. Kunkel.

VOL. 10 1959

The theory that rheumatoid arthritis may be a disease of metabolic origin rests to some extent upon its superficial clinical resemblance to two forms of arthritis, each one associated with a hereditary disturbance of metabolism. In neither is the precise relationship between the joint manifestations and the metabolic defect clearly understood. I refer to gouty arthritis and to ochronotic arthritis. The latter may be a disabling feature of alkaptonuria, which has recently been shown to be due to an inheritable defect in a single enzyme system.[62] Metabolic studies have thus far failed to demonstrate specific abnormalities in rheumatoid arthritis, with the possible exception of a diabetic type of glucose tolerance curve first studied by Pemberton[63] during World War I. This abnormality still remains unexplained, although it is assigned by some to the altered liver function which is found in a sizable proportion of rheumatoid patients.[64]

Hench and Kendall's discovery[74] in 1949 of the therapeutic action of cortisone in rheumatoid arthritis led naturally to renewed exploration of an endocrine factor in the pathogenesis of the disease. Before this time a role of the endocrine system had been suggested by bits of evidence, including the low basal metabolism found in a proportion of rheumatoid patients and the apparent increased susceptibility to the disease in women at the time of the menopause. It is now generally accepted that rheumatoid arthritis is not the result of adrenocortical insufficiency, although preliminary observations have shown quantitative and qualitative abnormalities in steroid excretion.[65] Histologic examination of endocrine organs has thus far not been revealing, with the exception of one unconfirmed study purporting to show specific changes affecting the cells of the anterior pituitary.[66] I might mention under this heading Selye's theory that the rheu-

matic diseases are diseases of adaptation and result from the excessive output of the electrolyte-regulating hormone by the adrenal cortex compared with a diminished output of so-called glucocorticoids, which are antirheumatic. This theory is based on somewhat controversial animal experiments and has not been confirmed by clinical investigative procedures.[67] I might add here that thus far the experimental production of arthritis in animals by bacterial, chemical, or hormonal agents has failed to throw light on the cause of rheumatoid arthritis in man.[68]

The last on my list of etiological theories, but by no means the most recent concept, is that psychologic factors are intimately concerned with the mechanism of rheumatoid arthritis. In fact, the earliest clinical accounts take note of the temporal relationship between emotional trauma and both the onset of the disease and exacerbations in its course. A consistent personality pattern has emerged from psychiatric studies of groups of rheumatoid patients[69] and the disease, along with peptic ulcer, hypertension, and bronchial asthma, has become classified as a psychosomatic disorder. Psychologic factors have been evaluated in children as well as in adults, with an attempt to dissociate those which arise as a consequence of the illness itself.[70] While there is at present an expanding interest in this aspect of rheumatoid arthritis, most investigators regard the psychologic factor merely as one of the complex set of factors that, even in disorders of known origin, are operative in bringing on the disease or its recurrence.

Treatment.—Since, as I have just outlined, the cause is unknown, no specific therapy directed toward an etiological agent can be available. This state of affairs in a disease does not, of course, preclude the discovery of a completely effective therapeutic agent, as, for example, the finding by Minot of the usefulness of liver in pernicious anemia. Thus far, no comparable remedy has come to light for rheumatoid arthritis, although Hench's momentous discovery in 1949 of the effect of cortisone has led to the availability of a number of agents capable of a suppressive effect on disease manifestations.

Space does not permit even a bare outline of the long and devious history of therapy in this disease. Until the early 1900's, the benefits of rest and exercise, heat and other modalities of what we now term physical therapy, various types of diet and a warm, dry climate, along with a host of medications, which included most consistently arsenic, iodides, quinine, and salicylates were cited. Although aspirin was introduced in 1899, its effectiveness as at least a symptomatic remedy was slow to gain acceptance. For the first 30 years or more of this century, it is fair to state that the infectious theory almost completely dominated therapeutic thinking in rheumatoid arthritis. Since no antibacterial agents were available, the approach was an indirect one. In the first place, the patient's resistance was to be raised by the general measures I have already mentioned. Next the source of the offending bacteria was to be eliminated by the removal or treatment of foci of infection, and finally bacterial vaccines, both stock and autogenous, were widely employed. The last two methods still have their advocates, in spite of the lack of evidence in support of their rationale and the negative results obtained in controlled therapeutic trials.

The treatment of rheumatoid arthritis in recent years may be divided into three aspects. The first is the use of the same general measures which have become more clearly defined and standardized and to which has been added a realization of the importance of the recognition and handling of the emotional factors concerned with the disease or created by it. It is now generally agreed that, regardless of what other treatment may be employed, a basic regime consisting briefly of rest suited to the stage and activity of the disease, a more than adequate diet, heat, exercises to preserve or improve joint and muscle function, prevention and correction of deformities by orthopedic measures, the relief of pain (chiefly by salicylates), and simple psychotherapeutic measures should be followed.[71] It should be mentioned here that no controlled studies are as yet available to testify to the efficacy of such a plan of management.

A second aspect of treatment is the use of agents which suppress disease activity. In addition to relief of pain, there is clinical evidence that aspirin or other salicylates actually exert an anti-inflammatory effect, as is the case in rheumatic fever. Phenylbutazone is another medication which is thought to exert a suppressive influence on disease activity in some patients but which is capable of producing much more serious toxic effects than the salicylates. The most potent suppressive agents are, of course, the corticosteroids, which may be counted on to exert at least a termporary anti-inflammatory effect in most rheumatoid patients. There is, however, no reason to believe that the disease course is altered by their use or that the fundamental pathologic process is completely arrested, no matter how intensive or prolonged their use. The unpleasant and at times serious side effects of these agents are well known. It has been stated that it is theoretically possible to create a substance of this nature that would cause only the desired effects and none of the undesirable.[72] In such case, we could expect to control most satisfactorily the manifestations of the disease but still might not appreciably alter its natural course.

I come finally to a third aspect of the treatment of rheumatoid arthritis, the search for a truly curative agent, one that can arrest the disease at whatever stage it may have reached and prevent anatomic or clinical progression. There is general agreement that this long-awaited development still belongs to the future although two remedies, gold salts and antimalarials such as chloroquine phosphate, are believed by some to have a definite if temporary effect on the disease course. Carefully controlled therapeutic studies with the use of modern biostatistical methods are indicated to determine the true value of these forms of treatment in a disease subject to unpredictable spontaneous remissions and exacerbations. One of the major present activities of the American Rheumatism Association is the development of a method of therapeutic testing which may be utilized to provide answers to such important questions.

CONCLUSIONS

It should be evident from what I have said that despite much thought and effort on the part of many workers during the hundred years since rheumatoid arthritis received its name, the ultimate goal—the cure or prevention of this

VOL. 10 1959

disease of unknown causation and of great economic and social significance—has not been achieved. To paraphrase the remarks of a recent historian of arthritis,[73] the history of the rheumatic disorders forces one to the conclusion that we are in no sense on a pinnacle looking down and back over a laborious pathway, up which medical investigators have fought. It is rather that we are now just at the foothill and just beginning to understand the nature of these afflictions.

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VOL
10
195

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OL.
10
959

THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

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VOL
10
195

RHEUMATOID arthritis is a clinicopathologic entity of unknown cause which may involve most if not all parts of the body but which is typically manifested by chronic progressive symmetrical inflammation of multiple joints, particularly those of the extremities. Despite this characteristic picture, none of the anatomic or clinical features recognized to date are specific and differentiation from other so-called connective tissue diseases depends on a combination of criteria established by convention.[1] Thus it is yet to be determined whether or not the nosologic entity of rheumatoid arthritis is etiologically distinct.

The pathogenesis of rheumatoid arthritis remains poorly established partly because the only well-known aspect of the lesions is their appearance after months or years of activity when the primary injurious process is obscured by nonspecific secondary changes. This review represents an effort to reconstruct the evolution of the anatomic features which characterize the disease by comparative analysis of: (1) classical lesions in various sites throughout the body, (2) early or highly active joint lesions and rheumatoid nodules, and (3) spontaneous and experimental lesions of known etiology which resemble those of rheumatoid arthritis. From a correlation of these findings with the clinical features of the disease a working hypothesis of the mechanism of tissue damage is proposed.

The lesions of rheumatoid arthritis, like those of rheumatic fever and other so-called connective tissue diseases, are typically focal, localized to discrete regions, and fall principally into three structural categories (Table I): (1) Inflammation of membranes which is predominantly exudative or proliferative in nature and exemplified by the inflammatory changes in the synovial tissue, serous membranes, the uveal tract of the eye, and the skin. This inflammatory process is largely responsible for the obliteration of joints in rheumatoid arthritis. (2) Focal connective tissue degeneration and necrosis typically associated with nodule formation, e.g., the subcutaneous nodules of rheumatoid arthritis. Other examples of such destructive lesions occur in the sclera, joint capsules,

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tendons, and tendon sheaths. In unusually fulminant cases, nodules may be present in serous membranes, the myocardium, the endocardium, and connective tissues throughout the body. Foci of necrosis in menisci and the wall of the aorta also fall into this general category, but are less space occupying in nature. (3) Segmental vasculitis—such lesions involve particularly venules and arterioles within nodular or membranous sites of inflammation. However, they may also occur unrelated to other lesions and involve larger vessels. The most pronounced effects of the vasculitis are exudation and ischemia. The histologic appearance of each of these three types of lesions will vary depending on its stage of development, location in the body, and intensity of the inflammatory process.

TABLE I. PRINCIPAL LESIONS OF RHEUMATOID ARTHRITIS

Inflammation of membranes
Synovitis
Serositis
Uveitis
Dermatitis
Focal connective tissue degeneration
Rheumatoid nodules
Focal necrobiosis of cartilage and aorta
Segmental vasculitis
Venulitis
Arteriolitis
Arteritis
Capillaritis

Let us consider first the classical articular lesions of rheumatoid arthritis which are characterized by proliferative inflammation of the synovial membrane. Nichols and Richardson[2] described the changes which account for the loss of motion in such chronically involved joints. In Fig. 1 two stages of ankylosis are seen in the same finger with advanced rheumatoid arthritis. Although usually distal interphalangeal joint involvement is less severe than that of the proximal joints, in this instance the distal interphalangeal joint has undergone bony ankylosis, while the proximal joint can still be recognized. It is to be noted that the inflammation subsides following complete immobilization by bony ankylosis. The proximal interphalangeal joint is bridged by fibrous tissue which has obliterated the synovial recesses and replaced the marginal cartilage. The active stage of cartilage resorption is characterized by ingrowth of chronically inflamed synovial tissue (pannus) from above, while similar granulation tissue may proliferate upward from the subchondral marrow spaces, and extend through the subchrondral plate to join the pannus in a pincer movement which may isolate bits of marginal cartilage (Fig. 2). Nichols and Richardson[2] named this process of joint destruction "proliferative arthritis" and emphasized that it was not specific for the idiopathic disease but could be produced to a varying degree by other irritating stimuli such as intra-articular fractures, gummas of the epiphysis, etc.

The most characteristic microscopic features of the synovial inflammation[1] are best seen in large joints such as the knee, and include the following: (1) marked villous hypertrophy; (2) proliferation of superficial synovial cells often with palisading; (3) marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with a tendency to form "lymphoid nodules"; (4) deposition of compact fibrin, either on the surface or interstitially; and (5) foci of cell necrosis. Although no one of these features is specific for rheumatoid arthritis, the combination of three or more of these features, in the absence of histologic evidence of other diseases, is of considerable diagnostic value. The "lymphoid nodules" in particular are highly distinctive especially when they are typically situated within the bulbous tips of hypertrophied villi and when they contain reaction centers like those seen in normal lymphoid tissue (Fig. 3).

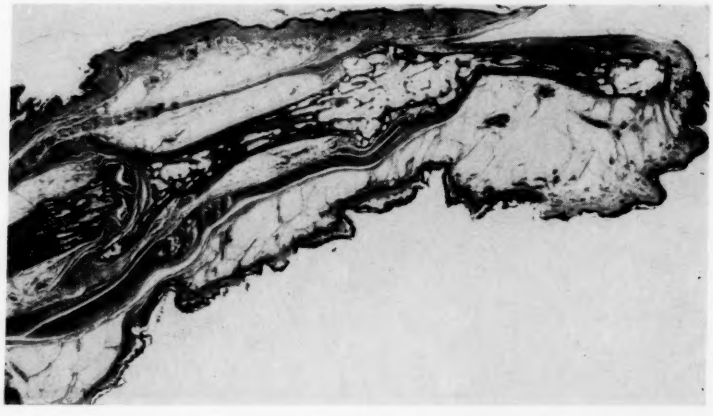

Fig. 1.—Advanced rheumatoid arthritis of finger. The proximal interphalangeal joint is bridged by dense fibrous adhesions and fibrous tissue has replaced most of the cartilage and some of the bone. The distal interphalangeal joint is obliterated by bony ankylosis which is associated with disappearance of the inflammatory reaction. (Hematoxylin and eosin stain ×2.5.)

The serositis and uveitis are usually less proliferative than the synovitis, but may result in effusions, fibrin deposition, and formation of adhesions.

The relation of cutaneous lesions such as psoriasis to rheumatoid arthritis remains controversial but regardless of any etiological relationship, the similarity between the articular lesions associated with psoriasis and those of rheumatoid arthritis suggests the possibility that the mechanisms of tissue injury in these conditions are analogous. It is therefore of interest to note that the epidermal thinning of psoriasis is localized over the inflamed capillary loops of the papillae while the rete ridges are hyperplastic. A similar tendency toward the presence of degenerative and proliferative changes side by side in relation to inflamed blood vessels is characteristic of the actively inflamed joints and the nodules of rheumatoid arthritis.

The focal connective tissue degeneration of rheumatoid arthritis is best seen in the subcutaneous nodules. These nodules have been considered to be

Fig. 2.

Fig. 3.

Fig. 2.—Destructive lesion at margin of interphalangeal joint. Synovial pannus has met in a pincer movement with granulation tissue extending up from the subchondral marrow and has isolated a cartilage fragment. Note the loss of chondrocytes from a large region of the hyaline matrix. (Hematoxylin and eosin stain ×200.)

Fig. 3.—Classic rheumatoid synovitis of knee with villous hypertrophy and lymphocytic nodules. Note reaction center in nodule at extreme right and thickening of blood vessels with round cell infiltration. (Hematoxylin and eosin stain ×60.) (From Kulka et al.: A.M.A. Arch. Path. 59:129, 1955.)

pathognomonic but may be difficult if not impossible to distinguish histologically from similar nodules occurring in rheumatic fever, disseminated lupus erythematosus, granuloma annulare, diabetes mellitus, or, at times, in patients without any evidence of other disease. Like the subcutaneous nodules of rheumatic fever, they may arise in a matter of hours and tend to occur at sites of pressure and mechanical irritation such as the elbows. In contrast to those of rheumatic

Fig. 4.

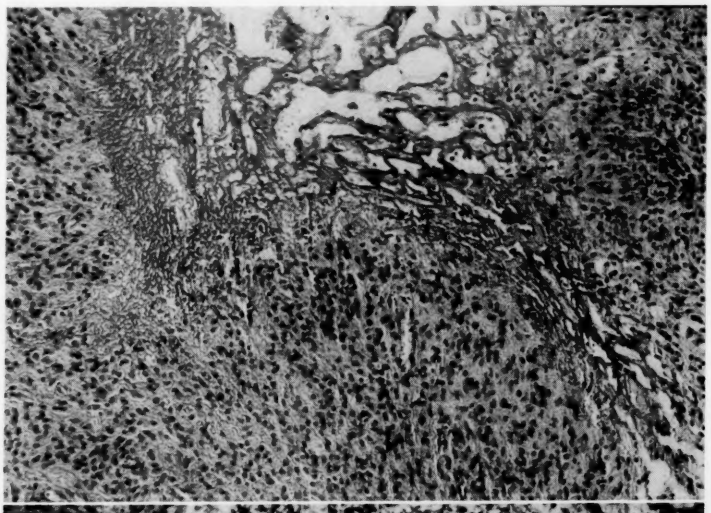

Fig. 5.

Fig. 4.—Classic rheumatoid nodule of subcutaneous tissue. The "geographic" central region of necrosis is permeated by coarsely reticular fibrinlike material and surrounded by hyperplastic connective tissue with radial palisading of innermost cells in places. (Hematoxylin and eosin stain ×200.)

Fig. 5.—Subcutaneous rheumatoid nodule with vascular connective tissue ("island") bridging a region of necrosis. (Eosin-methylene blue stain ×300.)

VOL. 10 1959

fever, however, the rheumatoid nodules usually persist for months or years. The classical microscopic features of a rheumatoid nodule consist of three zones (Fig. 4): (1) irregular, central regions of necrosis composed largely of amorphous eosinophilic debris, admixed with some fibrinlike material and remnants of collagen bundles; (2) surrounding zones of proliferating primitive fibroblasts typically arranged radially in palisade formation; and (3) peripheral chronically inflamed connective tissue. The characteristic "geographic" appearance of the necrotic regions is partly a result of inward-projecting "peninsulas" or "islands" of viable connective tissue which surrounds bundles of blood vessels as if it had

Fig. 6.—Aortitis beneath intimal plaque in sinus of Valsalva from a case of rheumatoid spondylitis. The histologic changes resemble those in syphilitic aortitis including medial and adventitial scarring, elastic tissue destruction, and obliterative endangiitis of vasa vasorum. (Verhoeff-van Gieson stain ×60.) (From Clark, Kulka, and Bauer: Am. J. Med. 22:580, 1957.)

survived by virtue of its proximity to blood supply (Fig. 5). It is interesting that of 7 patients with similar nodules but no evidence of rheumatic disease, 2 subsequently developed rheumatoid arthritis and 2 suffered from diabetes. This replication of a rheumatoid lesion in a disease which tends to produce obliteration of small blood vessels may not be entirely coincidental since a corresponding similarity to rheumatoid nodules may also be seen in certain infectious granulomas, e.g., gummas in which vascular obstruction is a feature of the basic pathogenetic process.

A particularly disabling form of focal connective tissue degeneration in rheumatoid arthritis is the tendinitis and tenovaginitis. Fig. 7 shows the gross appearance of severe inflammation of the extensor tendons of the wrist. The tendon sheaths have been dissected away and the tendons are seen to be surrounded and replaced in part by nodular masses of loose, edematous granulation tissue. Microscopically, focal regions within or on the surface of this inflammatory tissue often resemble the necrotic foci of rheumatoid nodules and these destructive changes account for the permanent stretching or the rupture of the involved tendons.[3] Elsewhere in the tendon sheath there is a chronic proliferative synovitis similar to that of joints and possibly resulting in part from irritation by tissue breakdown products liberated into the tendon sheath from foci of necrosis adjacent to the synovial surface.

The aortitis associated with rheumatoid arthritis[4] is another lesion characterized by focal connective tissue degeneration and bears an even closer resemblance to the corresponding lesion of tertiary syphilis than the rheumatoid nodule. The almost exclusive occurrence of this lesion in cases with spinal involvement suggests the possibility of an etiological difference from cases with peripheral joint involvement but might as well be a consequence of differences in sex incidence and other host factors. Thus the marked predilection of rheumatoid spondylitis for males is shared not only by rheumatoid aortitis but also by syphilitic and rheumatic aortitis. The similarity of rheumatoid aortitis to syphilitic aortitis includes both gross features (Fig. 8) such as aortic dilatation, tree-bark-like longitudinal wrinkling of the intima, and scarring of the semilunar valves with separation of the commissures, and microscopic changes (Fig. 6) such as focal elastic tissue and smooth muscle destruction in the media with replacement by granulation tissue, and proliferative endangiitis of vasa vasorum. The vascular obliteration involves both arterioles and venules at some distance from the degenerative lesions. In syphilis, the endarteritis has been considered to be of primary pathogenetic significance.[5]

The third basic type of lesion in rheumatoid arthritis, the segmental vasculitis, is the least well characterized since in most of the readily available anatomic material such vascular lesions are nonspecific and tend to be overshadowed by the articular lesions and nodules with which they are usually associated. Moreover, in uncomplicated, slowly progressive cases, the vasculitis is usually indistinguishable from secondary forms of vascular involvement which may occur in any chronic inflammatory process. Nevertheless, a growing body of evidence now indicates that vasculitis is a primary manifestation of rheumatoid arthritis as it is in other so-called connective tissue diseases.[6-13] The vascular lesions may resemble those seen in rheumatic fever, disseminated lupus erythematosus, and periarteritis nodosa, but show a particular predilection for venules (Figs. 17 and 18) which tend to become obliterated by necrosis and fibrin impregnation or endothelial proliferation (Figs. 11, 12, and 15). Thus the venulitis is readily recognizable as a primary lesion only in its active form as seen in the early developmental stages of both the articular lesions and nodules of which it is a common if not constant feature. Occasionally the venulitis is also found in long-standing rheumatoid lesions, but necrotizing arteritis and arteriolitis are

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Fig. 7.

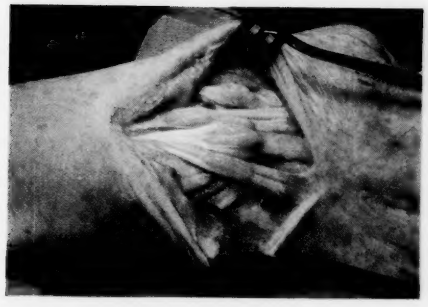

Fig. 8.

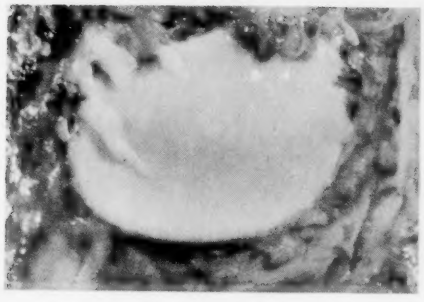

Fig. 9.

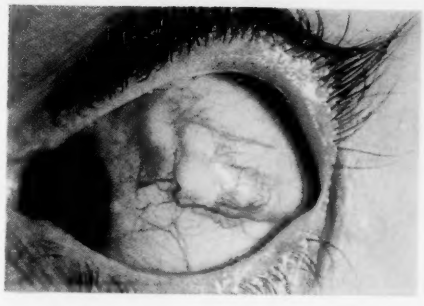

Fig. 10.

Fig. 7.—Tendinitis involving the extensors of the wrist. The tendon sheaths have been dissected away exposing nodular masses of granulation tissue which surrounds and partly replaces the tendons. (Courtesy Dr. Theodore A. Potter.)

Fig. 8.—Rheumatoid aortitis with aortic insufficiency. Note the resemblance to syphilitic aortitis including pearly thickening and longitudinal wrinkling of intima, involvement of coronary ostia, sagging of scarred valve cusps, and separation of the commissures. (Courtesy Dr. Walter Bauer.)

Fig. 9.—Anterior joint lining of knee in fulminant rheumatoid arthritis. The synovial villi are hypertrophied and some are hemorrhagic, while others are white and necrotic. The patellar cartilage is still almost uninvolved. (Courtesy Dr. Walter Bauer.)

Fig. 10.—Scleromalacea perforans. The reactive hyperemia stops at the margins of the nodular regions of necrosis. (Courtesy Dr. Walter Bauer.)

VOL
10
195

uncommon except in cases with fulminant disease in which the vasculitis is frequently disseminated and occurs independently of the extravascular lesions.

Lesions of rheumatoid arthritis which are not so readily classified into the three categories mentioned previously are focal myositis, peripheral neuritis, lymphadenopathy, splenomegaly, chronic inflammation of the salivary and lachrymal glands, and amyloidosis. All these lesions may also occur in other connective tissue diseases and as independent findings. The muscle and peripheral nerve lesions are characterized by juxtavascular focal lymphocytic infiltration and focal degeneration of the involved tissue.[14] Thus, their localization is suggestive of a vascular origin. In amyloidosis, the vascular system is again concerned in localizing the lesions since amyloid first appears in the form of subendothelial deposits. The increase in lymphoid and reticuloendothelial cells which is dominant in so many lesions of rheumatoid arthritis is particularly pronounced in the lymph nodes and spleen. Although this change appears to be nonspecific and reactive in nature, it is of interest since the cells involved are probably concerned in the production of plasma globulins and are thus a likely source of such blood factors as the rheumatoid factor, cryoglobulins, antibodies, and the substances concerned in the erythrocyte aggregation phenomenon (sludging of the blood). The chronic parotitis associated with Sjögren's syndrome[15] is dominated by intense lymphoid infiltration similar to that in Hashimoto's struma, where autoimmunization to thyroid protein has been implicated as a pathogenic factor.[16]

The cause of death in patients with rheumatoid arthritis is most often a result of intercurrent disease,[17] but as infections are being controlled by antibiotics, deaths from renal amyloidosis and from direct effects of rheumatoid lesions are becoming more common. Among the direct lesions of rheumatoid arthritis which occasionally cause death are pericarditis and myocarditis, aortitis with aortic regurgitation, and vasculitis which may become disseminated and result in ischemic necrosis or hemorrhage.

Considering this variety of anatomic lesions, is a single pathogenetic mechanism adequate to account for all basic manifestations of the disease or is it necessary to postulate three distinct disease processes in order to explain respectively the proliferative or exudative inflammation of membranes, the focal connective tissue degeneration, and the segmental vasculitis? Might the proliferative reaction of the joint lining be secondary to irritation by relatively inconspicuous foci of degeneration as suggested, for example, by the tendon lesion? Might the focal connective tissue degeneration be the result of ischemia caused by vasculitis as has been assumed in tertiary syphilis? If so, how are we to account for the involvement of avascular tissue such as heart valves and cartilaginous menisci? Some tentative answers to these questions have been obtained by anatomic study of biopsies from early lesions and postmortem material from occasional fulminant cases of rheumatoid arthritis who succumb to fatal manifestations of the disease during its highly active stage.

Let us attempt to trace backward the evolution of the deforming joint lesions. Destruction of cartilage is of particular importance since cartilage does not regenerate and the damage produced is irreversible. Since this destructive

process appears to take place only in close contact with inflammatory connective tissue such as synovial pannus it usually begins at the articular margins and advances centripetally. In active lesions, however, it is frequently apparent (Fig. 2) that the chondrocytes are necrotic well in advance of the pannus so that the synovial granulation tissue is mainly replacing devitalized hyaline matrix. The small blood vessels within the active pannus are often obliterated by intimal hypertrophy or fibrin thrombosis (Fig. 11), suggesting the possibility that the products of ischemic tissue might be concerned in the activation of local autolysis. Another significant feature is the frequent presence of compact fibrin or "fibrinoid" on the surface of the pannus and cartilage (Fig. 11). It is the failure of this material to resolve and its replacement by connective tissue which lead to adhesion formation and fibrous ankylosis. Such superficial fibrin impregnation of the cartilage may also occur ahead of the pannus[18] and could conceivably act as a diffusion barrier to impair the exchange of nutrients and metabolites between cells and tissue fluid. The association of the degenerative process in cartilage with fibrin impregnation and ischemia of adjacent connective tissue suggests a similarity to that in rheumatoid nodules.

The development of synovial inflammation appears to precede that of cartilage involvement. Thus, in Fig. 9, which shows the patella of a patient with fulminant rheumatoid arthritis of 2 years' duration, the cartilaginous articular surface is largely intact while the adjacent synovial membrane is markedly hypertrophied and some of the enlarged villi are hemorrhagic, or white and infarcted. The tissue breakdown products emanating from such necrotic regions could conceivably produce a diffuse secondary synovitis just as a myocardial infarct extending to the epicardium may result in diffuse fibrinous pericarditis.

The cause of the focal ischemia appears to be, at least in part, an acute venulitis and capillaritis with fibrin thrombosis, as demonstrated in lesions of less than 2 weeks' duration. Figs. 12, 13, and 14 show a synovial lesion of 7 days' duration as judged by the clinician.[18] We do not know whether this lesion is typical since none of comparable duration have become available for histologic

Fig. 11.—Advancing pannus with thrombotic venulitis in case of fulminant rheumatoid arthritis. Note that the synovial connective tissue is still intact. (Hematoxylin and eosin stain ×52.)

Fig. 12.—Synovitis of knee, 7 days' "duration." Note hyaline thrombi in three of the hyperplastic villi. (Hematoxylin and eosin stain ×206.)

Fig. 13.—Granulomatous focus from same synovial biopsy as Fig. 12. The arrow points to a capillary which is occluded by endothelial hypertrophy and surrounded by delicate strands of fibrinous exudate. Amorphous fibrin-like material permeates the synovial surface (*right border of margin*). (Hematoxylin and eosin stain ×334.)

Fig. 14.—Granulomatous region with focal necrobiosis from same biopsy as Figs. 12 and 13. Note disruption and ischemia of superficial synovialis (*right border of figure*) in passing from margin of granuloma (*top of figure*) to its center (*bottom border of field*). (Hematoxylin and eosin stain ×206.)

Fig. 15.—Subcutaneous nodule from same case as Fig. 9. Thrombosed venules can still be recognized within the region of necrosis in the right half of the field. (Hematoxylin and eosin stain ×84.)

Fig. 16.—Central region of "7-day-old" subcutaneous nodule. Venules and capillaries are in various stages of thrombosis and necrosis while most fixed cells of the intervening edematous connective tissue are hypertrophied and hyperplastic. (Hematoxylin and eosin stain ×334.)

Fig. 17.—Acute venulitis in "1-day-old" subcutaneous nodule. The vessel walls and perivascular tissue are infiltrated by delicate reticular fibrin and scattered leukocytes. There is little or no necrosis of fixed tissue cells and the vascular lumens are patent. (Hematoxylin and eosin stain ×134.)

Fig. 18.—Subcutaneous nodule of less than one day's "duration" from patient receiving a reduced amount of ACTH. Note the predominance of acute venulitis with intense neutrophil infiltration. (Hematoxylin and eosin stain ×84.)

Fig. 11.

Fig. 12.

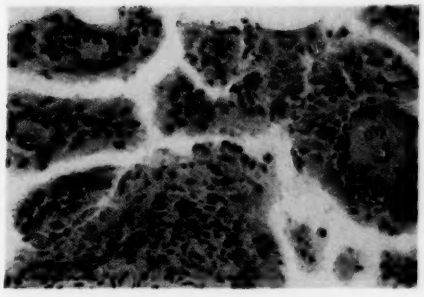

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Fig. 13.

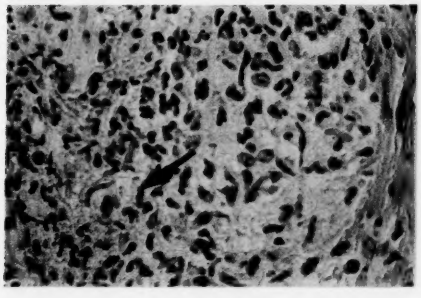


Fig. 14.

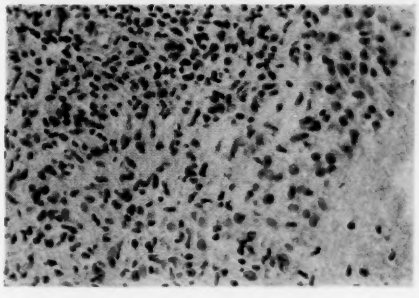


Fig. 15.

Fig. 16.

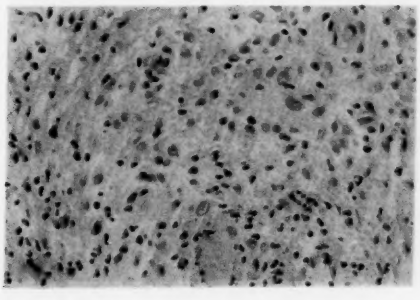


Fig. 17.

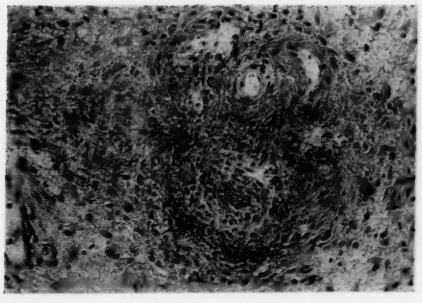
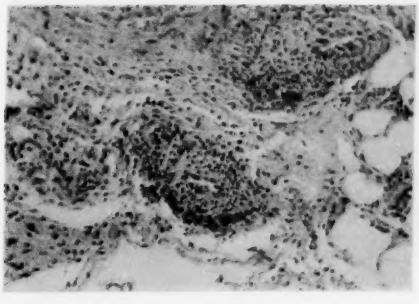


Fig. 18.



Figs. 11-18.—For legends, see opposite page.

VOL.
10
1959

study but the patient fulfilled the criteria of the American Rheumatism Association for definite rheumatoid arthritis. In contrast to the diffuse synovitis of older lesions the synovial proliferation and inflammatory cell infiltration were localized for the most part in scattered superficial granulomatous foci up to 2 mm. in diameter. Each focus was typically covered by a patch of fibrinous exudate and appeared to be centered about inflamed venules or capillaries infiltrated by fibrin and small mononuclear leukocytes (Fig. 13). Occasional inflammatory foci showed more marked tissue disruption associated with abnormally coarse collagen bundles and cellular necrosis (Fig. 14). Thus, early or highly active articular lesions differ from the classical proliferative arthritis in the frequent and possibly constant presence within the joint lining of active segmental vasculitis and focal necroses resembling those in the subcutaneous nodules. These findings suggest that the joint lesion of rheumatoid arthritis and rheumatoid nodules result from a single basic pathogenic mechanism of which vasculitis is a cardinal manifestation.

Rheumatoid nodules are better suited to morphogenetic study since they are relatively accessible to observation and biopsy during their early developmental stages. The scleral nodules demonstrate strikingly the gross appearance of the inflammatory process in vivo (Fig. 10). Note that the hypervascularity of the conjunctiva stops at the margins of the necrotic foci which are white and anemic. The anatomic basis for the ischemia appears to be widespread fibrin thrombosis of the minute blood vessels as can be seen in an active subcutaneous nodule in which necrosis has not yet obliterated the tissue outlines (Fig. 15). Is this thrombosis the cause or result of the connective tissue necrosis? Is the fibrinlike material which pervades the necrotic regions a degradation product of the injured connective tissue or is it a fibrinous exudate which has become admixed with the extracellular components of connective tissue and various products of necrosis? In attempting to answer questions such as these, the Massachusetts General Hospital Arthritis Study Unit obtained by intensive effort over a period of years 6 subcutaneous nodules varying from 7 days to less than 1 day in clinical duration. These lesions were consistently characterized by marked inflammation of many venules associated to a variable degree with fibrin thrombosis and deposition of similar fibrinous material within the vessel walls and surrounding tissue (Figs. 16, 17, and 18). Similar involvement of arterioles was inconstant and more localized. The only connective tissue change which occurred with regularity in the regions of vasculitis was edema. In 3 of the lesions there was also intense proliferation of primitive-appearing fibroblasts. Only 2 of the nodules showed well-defined regions of necrosis. Collagen changes were slight or absent in the 3 nodules which were of 3 days' or less duration. In Fig. 16 illustrating a "7-day-old" nodule, thrombosis of venules is prominent although the intervening connective tissue is predominantly intact and hyperplastic. In Fig. 17 from a "1-day-old" nodule, the eosinophilic material which emanates from several intensely inflamed venules still has the delicate reticular structure typical of inflammatory fibrin. Again, the fibroblasts are hypertrophied and hyperplastic, while necrosis is confined for the most part to leukocytes within the periendothelial zones where fibrin deposition is particularly

heavy. The exudative changes appear to be largely responsible for producing the space-occupying features of the lesion as shown by a clinical nodule which developed during reduction of ACTH therapy and was removed less than 24 hours after it was first noted (Fig. 18). In this instance the dominant histologic change is intense neutrophil infiltration of venules; cellular proliferation is minimal or absent and the connective tissue is characterized mainly by inflammatory edema. Thus, intense exudation from small blood vessels probably accounts for the rapid development of subcutaneous rheumatoid nodules while interstitial fibrin deposition and connective tissue proliferation help to maintain the space-occupying character of the lesions. The connective tissue necrosis and alteration of collagen appear to be secondary changes related in some way to increasing microcirculatory insufficiency which culminates in thrombosis of the terminal vascular bed.

To gain some insight into the process which initiates the lesions of rheumatoid arthritis, it may be helpful to consider diseases of known cause having a similar focal pattern of vascular and extravascular injury. Tertiary syphilis is of particular interest in this regard since it serves as a reminder that difficulty in the demonstration of microorganisms, minimal infectivity, and dominance of host factors as determinants of disease manifestations should not lead us to disregard the possibility of an infectious cause. Another type of infection which has yet to be excluded is that produced by a virus which may remain latent for long periods until a decrease in local or general resistance permits a lesion to develop, e.g., herpes simplex. Among the infectious diseases of animals, the arthritis of rats produced by the pleuropneumonia-like organisms[19] and swine erysipelas[20] are of particular interest because of their predilection for joint tissues although the lesions differ considerably from those of rheumatoid arthritis.

A noninfectious disease which may be analagous to rheumatoid arthritis as well as to periarteritis nodosa is serum sickness. This disease demonstrates the existence of an injurious mechanism which is intrinsic to the host but may be triggered by extrinsic factors such as an antigen. Might such a mechanism be triggered in ways other than by antigen-antibody interaction? There are indeed a number of human and experimental vascular lesions which resemble those of serum sickness and rheumatic diseases yet are not the result of hypersensitivity. Such lesions are those of the Shwartzman phenomenon,[21] those of local cold injury,[22] and those produced by various vasospastic agents such as Pitressin[23] and norepinephrine.[24] Other forms of focal necrotizing vasculitis are those produced by acute experimental hypertension,[25] by DOCA and sodium chloride after unilateral nephrectomy,[26] by rickettsia, e.g., Rocky Mountain spotted fever,[27] and by viruses, e.g., infectious arteritis of horses,[28] but in these latter lesions the possible participation of hypersensitivity remains to be excluded with certainty. In searching for a common denominator in the pathogenesis of these vascular lesions the frequent if not constant association with vasospasm deserves attention since there is some evidence relating functional as well as organic circulatory impairment to rheumatoid lesions (Table II). Thus vasospastic disorders frequently precede the onset of rheumatoid arthritis. Moreover, the

VOL. 10 1959

constant association of active rheumatoid arthritis with the erythrocyte aggregation phenomenon[29] would potentiate any tendency toward the development of local microcirculatory impairment.

Since a functionally induced microcirculatory disorder may be a primary pathogenetic factor, we have been investigating the role of ischemic changes in

Fig. 19.

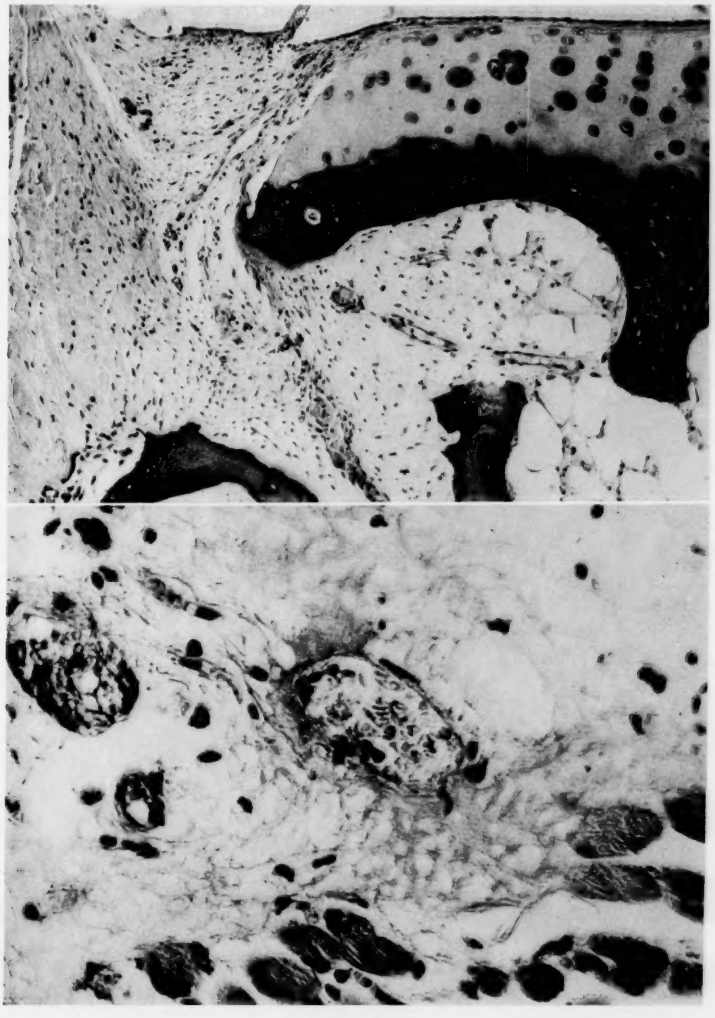


Fig. 20.

Fig. 19.—Interphalangeal joint of human toe 52 days after severe frostbite. Note defect of bone and cartilage at articular margin with ingrowth of fibrous pannus. Empty lacunae indicate necrosis of osteocytes. (Hematoxylin and eosin stain ×85.)

Fig. 20.—Segmental necrotizing venulitis in mouse ear after 7 days' exposure at 3° C. In the involved vessel wall, the nuclei are pyknotic and amorphous fibrin deposits extend into the surrounding tissue. (Hematoxylin and eosin stain ×410.)

TABLE II. EVIDENCE RELATING LOCAL CIRCULATORY IMPAIRMENT TO RHEUMATOID LESIONS

1. Necroses suggest ischemic origin.
2. Vasculitis parallels disease activity.
3. Vasospastic agents produce lesions resembling rheumatoid vasculitis.
4. Functional microcirculatory impairment may precede tissue damage.
5. Disease-precipitating factors (cold, emotional trauma, etc.) may cause vasospasm.

Fig. 21.

Fig. 22.

Fig. 21.—Capillary and venular stasis in mouse ear after 11 days' exposure at 3° C. Intravenously injected Evans blue dye (black in photograph) has entered the arterioles (*A*) and veins (*V*) but is absent from most capillaries and venules which are filled with erythrocytes (light gray in photograph). Note the segmental arteriolar spasm ("beading"). Arrow points to focal hemorrhage. (Rapid-frozen, unstained, cleared whole mount ×40; reduced 1/6.)

Fig. 22.—Arteriolar-venular shunting in mouse ear after 12 days at 3° C. Intravenously injected Evans blue dye has passed directly from arterioles (*A*) into adjacent venules (*V*) via short connecting capillaries (*S*), bypassing the main capillary and venular network. (Rapid-frozen, unstained, cleared whole mount ×90; reduced 1/6.)

cold injury.[30,31,32] The similarity of the articular lesions in frostbite to those in rheumatoid arthritis is illustrated in Fig. 19. A segmental venulitis (Fig. 20) associated with focal hemorrhage, fibrin deposition, necrosis, and thrombosis may be produced in the mouse ear without prior exposure to freezing by keeping the animals individually caged at 3° C. for 7 or more days.[31] The sequence of circulatory changes which lead to the development of vasculitis and ultimate gangrene was studied by a technique of instant freezing which fixes the blood vessels and their contents in a near lifelike state.[32] Circulating blood is distinguished from noncirculating blood by the presence of a dye such as Evans blue which is injected intravenously 1 minute prior to freezing. In this manner it can be demon-

strated that prolonged cold-induced segmental arteriolar spasm and generalized constriction of minute blood vessels are followed by capillary and venular stasis which progresses until plasma flow is confined largely to arteriolar arcades and major veins (Fig. 21). After a period of 7 or more days, arteriolar-venular shunts become established (Fig. 22), and massive thrombosis with connective tissue necrosis occurs soon thereafter. At present the role of similar microcirculatory changes in the pathogenesis of rheumatoid arthritis remains obscure, but it seems reasonable to assume that vascular factors are of fundamental importance in determining the focal character of the lesions and their distribution in the body.

In summary, the anatomic changes of rheumatoid arthritis correspond to a pattern of predominantly focal vascular and connective tissue injury which is similar to that of other so-called connective tissue diseases, certain infections such as tertiary syphilis, and serum sickness. A single basic pathogenetic process probably accounts for the diffuse inflammation of the lining tissue of joints, the focal degeneration of connective tissues exemplified by rheumatoid nodules, and the segmental vasculitis. This process is characterized less by the qualitative features of the tissue reaction than by its chronicity and by its predilection for joints and certain other body sites, particularly regions exposed to some mechanical stress and strain. A cardinal histologic manifestation of the disease is segmental inflammation of venules and other small blood vessels associated with marked exudation. The possible roles of blood factors and local vasomotor disturbances in initiating tissue injury present intriguing subjects for further study.

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VOL
10
195

THE BIOCHEMISTRY OF CONNECTIVE TISSUE

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OL.
10
959

MULTICELLULAR organization necessitates the development of an intracellular system that furnishes mechanical support and regulation of the *milieu intérieur*. In the simplest multicellular organisms, a gel-like matrix maintains structure and control of flow of materials to and from parenchymal cells. With increasing size and organization this matrix becomes more complex. Supply of nutrients and dissipation of metabolic products require a circulatory system as a channel between the exterior and the intracellular substance. Mechanical support no longer is achieved by a simple gel-like substance, but highly specialized structures such as tendons, bone, cartilage, and synovia appear. These many extracellular structures, derived from mesenchyme, comprise the connective tissues of the body. There is a close relationship between connective tissues and circulation with respect to embryology, morphology, composition, and function. A similar relationship exists with respect to reaction to injury.

Despite diversity of structure of specialized connective tissues, chemical similarity characterizes these tissues. The differentiation which accompanies morphologic specialization represents selective chemical adaptation utilizing common elements. Only in bone does serious modification occur with the addition of calcium salts.

This presentation will attempt to examine current knowledge of the biochemistry of connective tissue from three points of view: (1) chemical anatomy, (2) metabolism of connective tissues, and (3) functions and pathologic derangements.

CHEMICAL ANATOMY OF CONNECTIVE TISSUES

Fig. 1 is a sketch illustrating an idealized connective tissue. Between circulation and parenchymal cells are three elements unique to connective tissues: specialized connective tissue cells, structured fibers, and amorphous ground substance.

Two of the cell types have been linked to the specific biochemical properties of connective tissues. The fibroblast, including its specialized derivatives, such as the chondroblasts, osteoblasts, etc., has been clearly linked to the formation of collagen and ground substance acid mucopolysaccharides.[9,36,48,66] The mechanism by which fibers are elaborated has attracted considerable attention.[45]

The synthesis of collagen within fibroblasts is open to little question, but transformation to fibers remains a fascinating puzzle. Interesting is the nature of the specialization of fibroblasts to produce individual polysaccharides in special localizations. At least eight different acid mucopolysaccharides have been described. These occur singly or in mixtures at specific locations. Differentiation of races of cells results in restricted synthetic potentialities.

The mast cell which contains heparin, histamine, and 5-hydroxytryptamine has been studied extensively. The release of these substances by a variety of stimuli has led to speculation regarding the physiologic importance of this cell. That the metachromatic granules of mast cells contain heparin and that mast cells synthesize heparin seems established.[3,91] Cells resembling mast cells are produced by inclusion within fibroblasts of polyanionic substance.[41] The earlier suggestion[2] that mast cells are responsible for formation of other acid mucopolysaccharides has found no direct experimental support.

Collagen fibers assume a wide variety of configurations in connective tissues. Unknown are the physical and chemical factors which result in such contrasting structures as the reticular fibers of the spleen and the coarse oriented bundles of tendon. The fine structure of collagen has been extensively described.[39] Fig. 2 illustrates the characteristic electron microscope appearance of collagen fibers.

TABLE I. AMINO ACID COMPOSITION OF NATIVE UNLIMED COLLAGEN

AMINO ACID	N AS PER CENT PROTEIN N	GRAM RESIDUES PER 100 GM.	MILLIMOLES PER GRAM	ASSUMED NUMBER OF RESIDUES	APPARENT MINIMUM MOLECULAR WEIGHT
Amino nitrogen	2.5	——	0.33	——	——
Glycine	26.3	19.9	3.50	136	38.880
Alanine	8.0	7.6	1.06	41	38.580
Leucine } Isoleucine }	3.2	4.8	0.42	17	39.950
Valine	2.2	2.9	0.29	11	37.620
Phenylalanine	1.9	3.7	0.25	10	39.600
Tyrosine	0.6	1.3	0.08	3	37.620
Tryptophan	0.0	0.0	0.00	——	——
Serine	2.5	2.7	0.33	13	39.130
Threonine	1.5	2.0	0.20	8	40.160
Cystine	0.0	0.0	0.00	——	——
Methionine	0.4	0.7	0.05	2	37.640
Proline	9.9	12.7	1.32	51	38.760
Hydroxyproline	8.0*	12.1	1.07	41	38.580
Lysine	4.7	4.0	0.31	12	38.400
Hydroxylysine	1.2	1.1	0.08	3	37.680
Arginine	15.3	7.9	0.51	20	39.380
Histidine	1.2	0.7	0.05	2	37.640
Aspartic acid	3.6	5.5	0.47	19	39.750
Glutamic acid	5.8	10.0	0.77	30	38.910
Amide nitrogen	3.5	——	0.47	18	38.740
Total found	99.8	99.6†	10.76†	419	38.730 (mean)

*Determined on gelatin.
†Excluding amide nitrogen.

VOL.
10
959

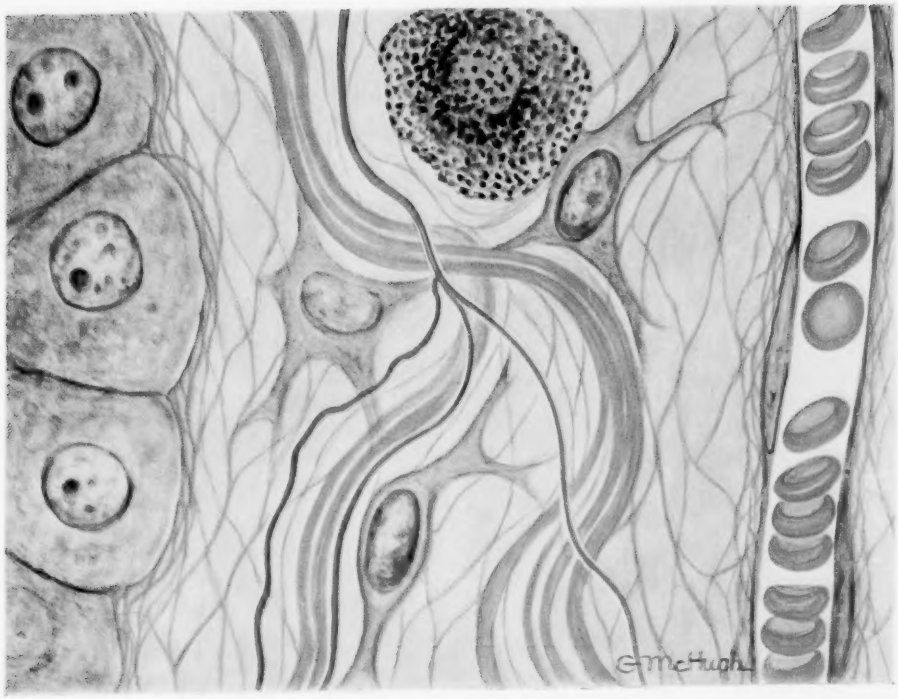

Fig. 1.—A schematic representation of an idealized connective tissue.

VOL.
10
1959

The typical banded appearance has been observed in collagens of widely varying origins. Equally typical of collagen fibers is the x-ray diffraction pattern. The amino acid composition of collagen is detailed in Table I.[40] The high glycine and proline content and the unique presence of hydroxyproline (in animal proteins) are hallmarks of collagen. Collagens of other phyla, which exhibit similar x-ray and electron microscope patterns, vary in amino acid composition.[31] The exact structure of the collagen molecule remains a matter of conjecture but current conceptions are of a molecule composed of three helical strands. Fig. 3 illustrates structures recently proposed.[82] A detailed discussion of these structures is beyond the scope of this paper, but this figure illustrates the three-helical structure that has been proposed. The two structures on the left are two different possible arrangements while that on the right illustrates the general configuration of the helices.

Fig. 2.—Electron micrograph of collagen fibers teased from guinea pig Achilles tendon in water. (The photograph was kindly supplied by Drs. Alan Hodge and Francis O. Schmitt of the Massachusetts Institute of Technology.)

The chemical and biologic understanding of collagen has received considerable impetus from the recognition of soluble forms of collagen. The demonstration of "acid soluble collagen" (originally called procollagen)[75,76] revived interest in the original demonstration[71] of the existence of acetic acid soluble collagen. More recent studies[30,73] have focused attention on the "neutral salt soluble" collagen. Numerous studies have established that soluble forms of collagen are converted to typical collagen fibers by variations in salt concentration, pH, temperature, and other additives.[32-34] Under certain conditions collagen may be transformed to structures different from those present in natural materials.[94] The exact nature of an individual collagen molecule is not yet clear, nor is the nature of the transition of soluble collagen to the collagen fibril.

Doty and co-workers[5,6,20] have studied the molecular parameters of soluble collagen. This "tropocollagen" molecule is highly asymmetric with a molecular weight of 350,000, length of 3,000 A°, and a diameter of 13.5 A°. These dimensions are approximately the same for ichthyocol, calf skin, and cod skin soluble collagens. Similar measurements have been made for rat skin soluble collagen[77] and rat tendon soluble collagen.[74]

Knowledge concerning both the chemistry and biology of elastin fibers is limited. Elastin has an amino acid composition strikingly different from collagen and characterized by a low content of polar amino acids.[16,53] No characteristic spacing is observed in the electron microscope and no evidence of orientation of the unextended fiber is evident from x-ray diffraction studies. The mechanism of biologic formation of elastin is poorly understood. No soluble tissue precursor of elastin has been isolated although some success at solubilization by chemical means has been achieved.[79,80] The claim that collagen and elastin fibers are interconvertible seems highly unlikely on chemical grounds. The demonstration of an enzyme in pancreas, elastase, which hydrolyzes elastin, has given impetus to the study of elastic tissues.[4] Unlike the case of collagen, there is no evidence of regeneration of elastic fibers. It is obvious that an understanding of the changes in connective tissue will require a much greater understanding of the chemistry and biology of elastic tissues.

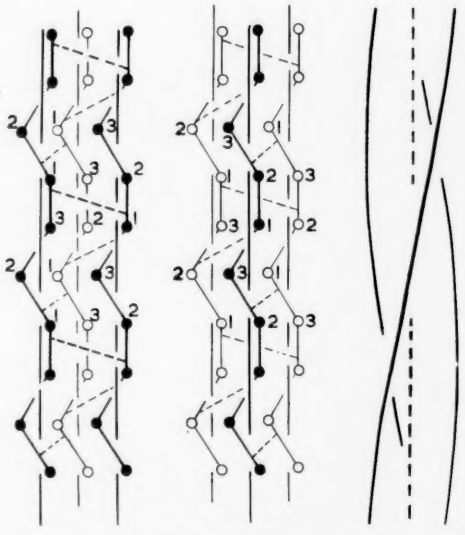

Fig. 3.—An illustration of the possible arrangement of the 3 chains of collagen in helix. The figure to the left is a structure proposed for collagen I and that in the middle for collagen II. The figure to the right shows the turn of the right-hand helices around a common axis indicated by a dotted line.

The connective tissue fibers are imbedded in an amorphous matrix, the ground substance. The relative amounts of fibers and ground substance and the qualitative composition of ground substance varies widely in different connective tissues. At one extreme is the gel-like structure of vitreous humor composed almost exclusively of mucopolysaccharides, hyaluronic acid, with only small amounts of fine collagen fibrils. Similar in composition is synovial fluid. At the other extreme are tissues such as tendon and dermis consisting of dense collections of collagen fibers imbedded in small amounts of ground substance. The complete chemical composition of ground substance is unknown. It contains both materials in transit between cells and circulation and components unique to connective tissues.

The state of the soluble precursors of collagen in ground substance is uncertain, but extraction of soluble collagen by neutral salt solution indicates soluble precursors of collagen are probably present in ground substance. The high viscosity of soluble collagen solutions, due to marked molecular asymmetry, may account in part for the gel-like structure of ground substance. No soluble elastin precursors have been isolated. Ground substance also contains noncollagenous proteins. A portion of these are similar to those of plasma. The proteins bound to acid mucopolysaccharides will be considered with that group of substances.

A considerable body of evidence indicates that the acid mucopolysaccharides are responsible for some of the unique characteristics of ground substance. These compounds are anionic polymers containing alternating units of acetylated hexosamines and hexuronic acids. Fig. 4 illustrates the disaccharide repeating unit of chondroitinsulfuric acid-A.[14,15] The polysaccharide molecules consist of long chains of such repeating units linearly arranged.

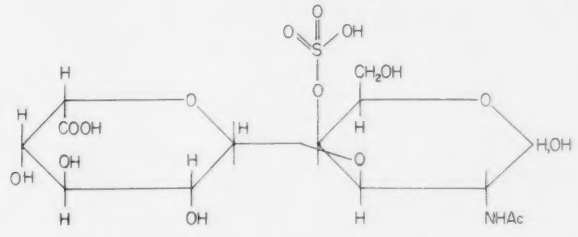

Fig. 4.—The disaccharide repeating unit of chondroitin sulfuric acid-A.

TABLE II. MUCOPOLYSACCHARIDES OF CONNECTIVE TISSUES

	AMINO SUGAR	URONIC ACID	SULFATE
Hyaluronic acid	N-acetylglucosamine	Glucuronic acid	−
Chondroitinsulfuric acid-A	N-acetylgalactosamine	Glucuronic acid	+
Chondroitinsulfuric acid-B (β-heparin)	N-acetylgalactosamine	Iduronic acid	+
Chondroitinsulfuric acid-C	N-acetylgalactosamine	Glucuronic acid	+
Chondroitin	N-acetylgalactosamine	Glucuronic acid	−
Keratosulfate	N-acetylglucosamine	(Galactose)	+
Heparin	Glucosamine (N-sulfated)	Glucuronic acid (?)	+
Heparin monosulfuric acid	Glucosamine	(?)	+

Connective tissue contains a number of acid mucopolysaccharides with varying chemical composition but similar structure. Table II indicates the composition of the known acid mucopolysaccharides. The chemical structure of several of these compounds has been firmly established in recent years, particularly due to the ingenious studies of Meyer and his colleagues. Hyaluronic acid occurs in a number of tissues and is particularly abundant in vitreous humor, synovial fluid, and Wharton's jelly. This nonsulfated polysaccharide forms long chains and is bound less firmly to protein than are the sulfated poly-

saccharides. Chondroitin, the one other nonsulfated polysaccharide, is at yet imperfectly characterized. It has been claimed to be an intermediate in the biosynthesis of chondroitinsulfuric acid.[14,15]

Chondroitinsulfuric acids-A and -C are found in greatest abundance in cartilage although they also occur in other tissues. There is a great similarity between these two substances, both in properties and in composition. Infrared studies[43,63] indicate that they differ only with respect to position of the sulfate ester group on the hexosamine molecule. Chondroitinsulfuric acid-C is present in the cartilage of elasmobranchs[72] while chondroitinsulfuric acid-A occurs in the cartilage of mammals. Chondroitinsulfuric acid-C does occur, however, in the *nucleus pulposus* of mammals.[78] Chondroitinsulfuric acid-B contains L-iduronic acid, in contrast to the presence of D-glucuronic acid in other acid mucopolysaccharides. Fig. 5 compares the structure of L-iduronic acid with that of D-glucuronic acid. Chemical studies[11,42] indicate that chondroitinsulfuric acids-A and -B differ only with respect to this variation in configuration, despite the striking contrast in physiologic activities of the two compounds. Chondroitinsulfuric acid-B, which has been isolated from a number of tissues, is a potent antithrombic substance.[37] Chondroitinsulfuric acids-A and -C are devoid of such activity. The contrast in antithrombic activity parallels the capacity of these compounds to bind certain polyvalent cations.[65] Chondroitinsulfuric acid-B has been isolated in large amounts from the urine of patients afflicted with the hereditable disorder, Hurler's syndrome.[17,18,68]

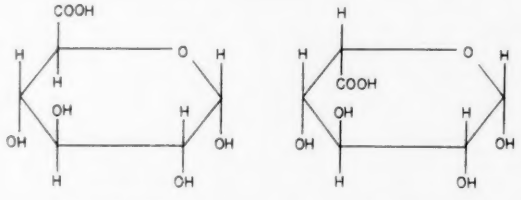

Fig. 5.—A comparison of the structures of L-iduronic and D-glucuronic acids.

Heparin is chemically imperfectly characterized. In contrast to the other sulfated mucopolysaccharides, it contains three sulfate groups per disaccharide repeating unit. The linkage between monosaccharide units appears to be alpha,[24] in contrast to the β-glycoside linkage of hyaluronic acid[110] and the chondroitinsulfuric acids.[14,15]

Heparin monosulfuric acid (heparitin monosulfate) originally discovered[48] as an impurity in preparations of heparin, has recently assumed an increasing importance. This substance is similar to heparin in certain properties (amino sugar, optical rotation) but contains less sulfate and an N-acetyl group, absent from heparin. The material heretofore studied is not a chemically distinct compound and may be a mixture of several substances.[12] Preliminary studies indicate that it is not comparable to heparin in anticoagulant activity.[38] This compound is excreted in large quantities in patients with the Hurler syndrome

and has been demonstrated as the storage material in tissues of a number of these patients.[17,18,68] It is possible that this is a precursor in the synthesis of heparin.

Keratosulfate differs from the other acid mucopolysaccharides by the replacement of the uronic acid by galactose.[67] The detailed structure of this compound is unknown, although preliminary studies indicate that the acetylglucosamine is substituted in the 3 position as is true of hyaluronic acid and the chondroitinsulfuric acids.[10] This polysaccharide was originally demonstrated in cornea but is also present in *nucleus pulposus*.[26]

Little is known regarding the state of mucopolysaccharides in tissues. Whether individual polysaccharides are specifically localized anatomically is unknown. Interpretations of biologic phenomena on the basis of gross analytical changes are unsatisfactory since specific qualitative changes may be important.

A protein complex of chondroitinsulfuric acid may be extracted from cartilage by mild procedures.[95] The composition, structure, and physical-chemical properties of this complex have been studied.[62,64] It was found to be an asymmetric molecule with a molecular weight of at least 4×10^6. The molecule contains approximately 62 chains of chondroitinsulfuric acid of molecular weight 50,000, and a protein content of approximately 20 per cent. It is suggested that the chondroitinsulfuric acid side chains are attached to a central protein core. Association between macromolecules also occurs. The protein has an amino acid composition which differs from that of collagen. Muir[70] has suggested that the polysaccharide residues are attached to the protein core through serine.

METABOLISM OF CONNECTIVE TISSUE

Little is known regarding the mechanism of biosynthesis of connective tissue proteins. Considerable effort has been focused on the finding that proline is a more efficient precursor of the hydroxyproline of collagen than is free hydroxyproline.[101,111] A similar state of affairs exists for the relationship between lysine and hydroxylysine.[81,97] The rate of turnover of collagen in tissues has been measured.[73] Insoluble collagen fibers are metabolized at an extremely slow rate. In contrast, acid soluble collagen and, to a greater extent, neutral salt soluble collagen turn over more rapidly.

Although insoluble collagen is metabolically stable, morphologic evidence leaves no doubt that collagen is rapidly destroyed and removed. Elucidation of this mechanism is important to explain the fragmentation and destruction of collagen evident in a variety of diseases.

Insight into the metabolism of acid mucopolysaccharides is increasing rapidly. Earlier studies were confined to investigation of hydrolytic enzymes, primarily hyaluronidases. Recent work has clarified the mechanism of action of hyaluronidases. Testicular hyaluronidase splits the hexosaminidic bonds of hyaluronic acid and chondroitinsulfuric acids-A and -C to form a mixture of oligosaccharides, the tetrasaccharide predominating.[109] Bacterial hyaluronidase, however, produces an unsaturated disaccharide on rupture of the glucosaminidic bond of hyaluronic acid.[58] A microorganism, *Flavobacterium heparenium*, has

been found which produces adaptive enzymes which split other mucopolysaccharides of mammalian connective tissue.[49,50] Leech hyaluronidase degrades hyaluronic acid by splitting the glucuronidic bond.[59]

The physiologic importance of hyaluronidase remains obscure. There is no evidence that these enzymes are involved in the normal catabolism of tissue mucopolysaccharides since hyaluronidase activity has not been conclusively demonstrated in mammalian tissues other than testes.

The pathway of biosynthesis of acid mucopolysaccharides is becoming rapidly clarified. A great deal of the recent progress has resulted from discovery of the role of uridine nucleotides in polysaccharide synthesis.[7,8,54-57]

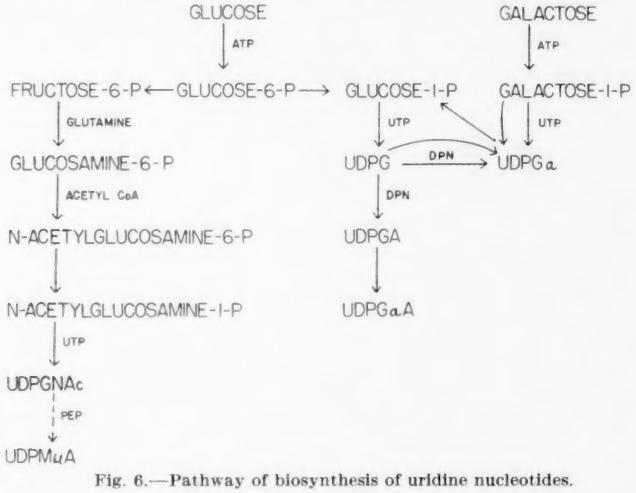

Fig. 6.—Pathway of biosynthesis of uridine nucleotides.

Fig. 6 represents the metabolic pathway for the synthesis of the uridine nucleotides that are intermediates in polysaccharide synthesis. The elucidation of this pathway has already furnished information of profound importance in many diverse aspects of medicine. The metabolic defects in galactosemia and icterus of the newborn have found explanation in these studies.[47,92,93] All of the enzymatic steps involved in the formation of the uridine nucleotides concerned with acid mucopolysaccharide synthesis have not been demonstrated in connective tissues. It seems probable, however, that this scheme is of general validity.

Fig. 7 indicates the scheme for the synthesis of a variety of naturally occurring carbohydrates from uridine nucleotides. This is incomplete. Undoubtedly, many other biologically important compounds will be added to this list. The lower right-hand part of Fig. 7 shows the pathway of synthesis of three important disaccharides: sucrose of plants, lactose of milk, and trehalose.[22,25,56] Uridine diphosphoglucose is the key intermediate since it has already been demonstrated to be the precursor of cellulose,[28] glycogen,[57,83,108] and glucan,[23] a polysaccharide found in vegetables. In addition, uridine diphosphoglucose may be oxidized to uridine diphosphoglucuronic acid, the intermediate for uronide formation.[21,102]

Uridine diphospho-N-acetylglucosamine is of importance not only for the formation of hyaluronic acid but also chitin,[29] the polymer of the exoskeleton of

insects and walls of molds. In addition, it appears to be the precursor of uridine diphosphomuramic acid necessary for bacterial wall synthesis.[103]

The biosynthesis of hyaluronic acid may be conveniently studied by the use of a strain of Group A streptococci since the capsular polysaccharide of this microorganism is indistinguishable from that of mammalian connective tissues. A cell-free preparation has been obtained on sonic disruption of this microorganism which synthesizes hyaluronic acid from uridine diphospho-N-acetylglucosamine and uridine diphosphoglucuronic acid in the presence of magnesium ions.[19,61] The activity is not sedimented by centrifugation of 10,000 × g but is sedimented at 100,000 × g. No evidence has been obtained for the participation of more than one enzyme or for the requirement for a polysaccharide primer.

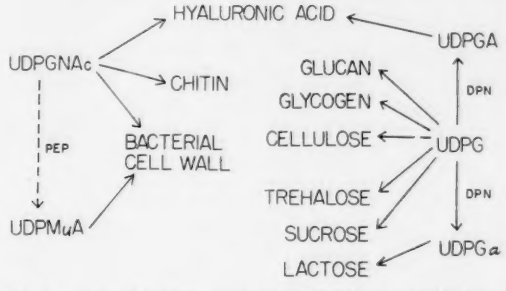

Fig. 7.—Role of uridine nucleotides in polysaccharide synthesis.

The biosynthesis of hyaluronic acid is of special interest since it involves the interaction of two uridine nucleotides by a mechanism which alternates groups. There are present numerous substances in nature whose biologic properties and specificities are dependent upon orderly biosynthesis. The availability of a partially purified enzyme which synthesizes hyaluronic acid should open the possibility for determination of the manner in which such a feat is achieved.

The mechanism of synthesis of the sulfated mucopolysaccharides is less well understood. The incorporation of radioactive sulfate into chondroitinsulfuric acid by an enzyme obtained from the epiphyses of chick embryos has been demonstrated.[13] The participation of "active sulfate," PAPS, apparently is similar to that in other sulfation reactions which have been elucidated.[60] Whether de novo synthesis of chondroitinsulfuric acid occurs in this system is not yet clear. The incorporation of radioactive sulfate into heparin by a homogenate of a mouse mast cell tumor has been shown.[100] Recent studies[105] suggest sulfation occurs after polysaccharide formation.

Many questions remain unanswered regarding the pathway of acid mucopolysaccharide biosynthesis. The mechanism of origin of L-iduronic acid is not clear, but studies indicate that it arises from glucose without scission of the hexose chain.[84]

The relationship of the biosynthesis of acid mucopolysaccharides to that of the accompanying protein is intriguing. The two moieties turn over at similar rates in rat costal cartilage.[35]

The use of isotopic precursors has facilated the study of the rate of turnover as well as the localization of acid mucopolysaccharide in many tissues. For the most part such studies have been carried out with S^{35} and have led to a voluminous literature concerned with localization of this isotope in tissues.

An extensive set of investigations has been performed on the rate of metabolism of acid mucopolysaccharides in the skin of rats and rabbits.[85-87] C^{14}-labeled acetate, C^{14}-labeled glucose, and S^{35} were used to measure the turnover rate of the various portions of the mucopolysaccharide molecule. Since skin contains both hyaluronic acid and a mixture of chondroitinsulfuric acids, the turnover rates of both compounds were measured simultaneously. Hyaluronic acid is metabolized more rapidly than is chondroitinsulfuric acid. The similarity of half-life times obtained with acetate-l-C^{14}, glucose-U-C^{14}, and S^{35} suggests the complete turnover of the polysaccharide molecule. With these techniques it was discovered that hydrocortisone inhibits mucopolysaccharide turnover.[89] A marked inhibition of mucopolysaccharide metabolism was demonstrated in alloxan diabetic rats.[88] This impairment was restored by insulin. These findings are of interest with respect to decreased resistance to infection, failure of wound healing, and accelerated vascular degeneration in diabetes mellitus. More recently, evidence has been obtained that growth hormone may have a selective effect on mucopolysaccharide metabolism, restoring in hypophysectomized rat skin the metabolism of the sulfated mucopolysaccharides, but not that of hyaluronic acid.[89]

The rapid evolution of knowledge regarding the intermediary metabolism of polysaccharides gives promise that a more thorough understanding of the pathways of biosynthesis and degradation of acid mucopolysaccharides of connective tissues may be at hand.

FUNCTIONS AND PATHOLOGIC DERANGEMENTS OF CONNECTIVE TISSUES

The role of the ground substance as a regulator of cell environment has been emphasized by a number of workers. This possibility is perhaps best considered in relationship to certain physical-chemical properties. Fig. 8 depicts a model of a mucopolysaccharide-protein-complex as it may exist in tissues. Long randomly coiled chains of mucopolysaccharides are attached to a central protein core. For purposes of convenience of illustration, only a small segment of the molecule is shown and the length of polysaccharide side chains is much reduced. Each repeating disaccharide unit has two negative charges representing sulfate and carboxyl groups. Clustered about these charges are bound cations (*red*) and a sufficient number of anions (*yellow*) to maintain electrical neutrality. (The water molecules represented by the blue background are also condensed about these chains to indicate their effect on holding water.) The quantitative importance of these effects in physiologic equilibria and pathologic disturbances remains to be evaluated. It is possible that such a mechanism may be of importance in establishing both qualitative and quantitative ion gradients in specific areas. Histochemical evidence indicates that basement membranes contain a condensation of acid mucopolysaccharides.

OL.
10
959

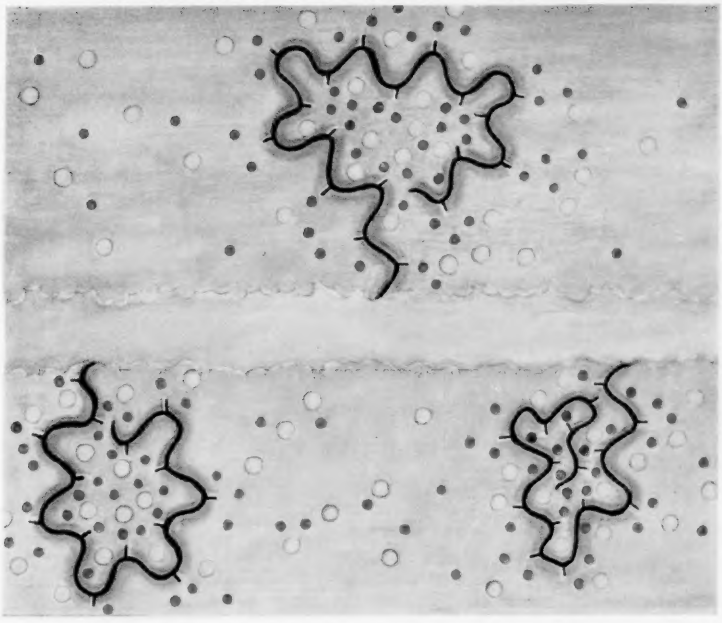

Fig. 8.—A portion of the protein mucopolysaccharide complex. The center core represents the protein. The wavy black line represents the polysaccharide chain. The red dots are sodium ions and the yellow dots are chloride ions. The blue background represents the water of the milieu.

VOL.
10
195

The function of connective tissues in maintaining structural integrity of tissues is obvious. The details of organization at a microscopic level remain to be ascertained. Gersh and Catchpole[27] introduced the concept that depolymerization of acid mucopolysaccharides is an accompaniment of a wide variety of physiologic and pathologic changes. Although the histochemical evidence was inadequate for the determination of depolymerization, their studies suggest changes in the physical-chemical structure of ground substance. The release of mucopolysaccharides from protein complexes may account for marked physical alteration of tissues. A striking demonstration of this possibility was the finding of the collapse of the rabbit ear as a result of intravenous injection of papain.[107] This phenomenon results from the hydrolysis of the protein which binds the mucopolysaccharides in tissues. It has been shown that plasmin hydrolyzes the protein that binds acid mucopolysaccharides.[52] It is possible that destructive lesions in connective tissue may result from the local release of proteolytic activity by the activation of proteolytic enzymes. Pretreatment of tendon with hyaluronidase increases the solubility of collagen.[44] The association of the chondroitinsulfuric acid–protein complexes with soluble collagen has been demonstrated.[64] The destruction of the polysaccharide-protein complex may make collagen fibers more vulnerable to fragmentation and dissolution.

We have been thus far concerned with general properties of connective tissue polysaccharides. Specific properties of the individual polysaccharides require more attention. Chondroitinsulfuric acid-B is of particular interest in this respect. It is present in much larger quantities in tissues than is heparin. Under appropriate conditions this compound is a potent antithrombic substance while under others it antagonizes the normal antithrombic activity of plasma.[37] Studies on the mechanism of the generalized Schwartzman phenomenon suggest that an altered fibrinogen is deposited in tissues as fibrinoid.[106] Since there is evidence that fibrinoid contains acid mucopolysaccharides,[1] it is reasonable that the deposition of fibrinoid depends upon changes in quantity, binding, or physical-chemical state of acid mucopolysaccharides. Further investigation of this possibility appears warranted.

The role of connective tissue polysaccharides in lipid metabolism is a subject too extensive for this review. Widespread attention has been focused on clearing action of heparin. Less is known about the possible role of the state of connective tissue components in determining deposition of lipids in tissues.

Relatively little is known regarding the possible role of qualitative and quantitative changes in the composition of connective tissue. The studies of Sobel and co-workers,[99] although subject to serious technical limitations, suggest a decrease in mucopolysaccharide to collagen ratio with age. More definitive has been the recent findings that the ratio of glucosamine to galactosamine increases with age.[51,96] This observation finds explanation in the report of Meyer and associates,[69] that rib cartilage in the human adult contains a large proportion of keratosulfate in contrast to its absence in similar cartilage from newborns. Even larger amounts of keratosulfate were obtained from cartilage of patients with Marfan's syndrome. Of interest is the report that such patients excrete large amounts of hydroxyproline,[98] a finding suggesting a disturbance in collagen metabolism.

The changes in the qualitative composition of connective tissue with age raise important possibilities for the explanation of degenerative changes. The substitution of keratosulfate for chondroitinsulfuric acid-A and the decrease in proportion of polysaccharide to collagen may be responsible for alteration in the functions of ground substance both in the control of the *milieu intérieur* and the maintenance of the mechanical properties of connective tissues.

That metabolic defects of connective tissue polysaccharides result in marked distortion is illustrated by the Hurler syndrome.[17,18,68] The nature of the metabolic defect which leads to the accumulation and excretion of large amounts of two different acid mucopolysaccharides is still obscure. Presumably such a hereditable disorder should find explanation in a single genetically determined enzymatic defect.

Attempts to study biochemical changes in rheumatic diseases so far have been limited. A number of studies of the physical-chemical properties of synovial fluid in rheumatoid arthritis suggest a decrease in the molecular weight of the hyaluronic acid.[104] The relationship of this observation to the specific pathology of the disease is not clear.

SUMMARY

Study of the biochemistry of connective tissues has progressed rapidly in recent years. Considerable progress has been made in the understanding of the structure of collagen fibers and their metabolism while less is known regarding elastic fibers. The chemistry and metabolism of acid mucopolysaccharides is becoming clear.

These studies already point the way to new approaches to the study of connective tissue disease. It seems likely that greater insight into both the physiology and pathology of connective tissue soon may be at hand.

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OL.
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959

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VOL
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VOL.
10
1959

IMMUNOLOGIC ASPECTS OF RHEUMATOID ARTHRITIS

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VOL
10
195

THE possibility that rheumatoid arthritis has as its basis an immunologic mechanism has long been entertained. Fragmentary clinical and pathologic evidence has been gathered, but equally cogent arguments against such a hypothesis can be and have been cited. The problem is obviously not settled, but recently some new evidence has appeared that perhaps favors an immunologic mechanism and it is with this new material, accumulated in a number of different laboratories, that this report is primarily concerned.

The first point to be considered is the close relationship of rheumatoid arthritis to another disease, lupus erythematosus, where overwhelming evidence for an altered immunologic process is accumulating. This is a disease with widespread manifestations but with arthritis as an important feature. The cardinal laboratory manifestation of lupus erythematosus is the L.E. cell phenomenon, which is a reaction that has aroused a great deal of interest and which is widely used as a laboratory test for this disease. A factor is present in the serum of these patients which causes peculiar changes in the nuclei of cells. These nuclear changes are the characteristic manifestations of the L.E. cell and are readily observed by blood smear slide tests. This test, discovered by Hargraves at the Mayo Clinic in 1949, has impressed investigators more and more with its specificity and close relationship to the disease, lupus erythematosus. Typical L.E. cells are formed upon the addition of serum from a patient with lupus erythematosus to a suspension of white blood cells from normal serum. Large, swollen purple-staining masses called lupus bodies are specifically produced by the sera of these patients. Some of these bodies may be visible free in the medium, others are phagocytized by leukocytes, causing the cell's own nuclei to be moved to the periphery of the cell.

A number of patients with rheumatoid arthritis show the L.E. factor in their sera and give a positive L.E. test.[4] The exact incidence is not settled but appears to be higher than in any other disorder except lupus itself and suggests a relationship. In addition, patients with long-standing rheumatoid arthritis may also develop many of the characteristic clinical manifestations of lupus.[18] The reverse is also true, and young girls with classical lupus may show a pro-

gression to an arthritic condition that is indistinguishable from rheumatoid arthritis. The two diseases, although clearly differentiated in their most classical form, have many features in common and transitional cases are often observed in which a single individual possesses manifestations of both conditions at the same time. This has been brought out more emphatically recently through the use of the rheumatoid factor tests. These tests, which show considerable specificity for rheumatoid arthritis, will be described in more detail later. High titers in these reactions, however, may be observed coexisting with strongly positive L.E. tests. These patients constitute a real dilemma to rheumatologists and the latter are constantly asking those of us who work primarily in the laboratory for aid in establishing a diagnosis of either lupus erythematosus or rheumatoid arthritis. We have been unable to help them in most instances, and it appears now that such patients on the basis of both their laboratory and clinical characteristics appear almost to have hybrid forms of the two diseases.

OL.
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959

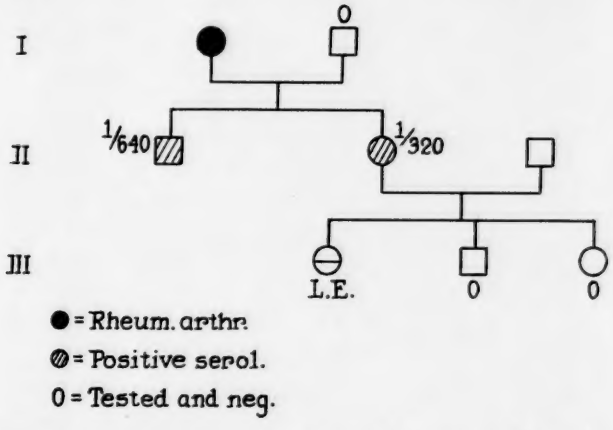

Fig. 1.—Pedigree of a patient with lupus erythematosus (L.E.) showing rheumatoid arthritis and positive serologic tests for rheumatoid factor in maternal side.

Perhaps the most clear-cut evidence suggesting a relationship between the two disorders has appeared from genetic studies. Tracing of the families of individuals who are suffering from lupus erythematosus has been particularly rewarding. Dr. Holman[7] has been carrying out such studies for several years and he has been struck with the high incidence of other conditions, particularly rheumatoid arthritis, in the relatives. Laboratory studies of these families of lupus patients have revealed only a few members with positive L.E. tests, but it is the rheumatoid factor tests that have furnished the most interesting results. Some of the relatives not only have positive tests, but show high titers by a number of the different tests available. Fig. 1 illustrates the genetic chart of one such family.

Having thus described some of the many features linking rheumatoid arthritis with lupus erythematosus, a powerful argument for an immunologic basis for rheumatoid arthritis is gained from closer scrutiny of lupus erythematosus. The evidence that the latter represents a primary immunologic disorder is very

considerable and is derived from many different fields of investigation. Certain of the patients are sensitive to drugs such as sulfonamides and penicillin, and administration of such drugs can set off the major clinical manifestations of this disease. Antibodies to the patient's own red cells, causing hemolytic anemia, have been frequently described. Antibodies to leukocytes and platelets also

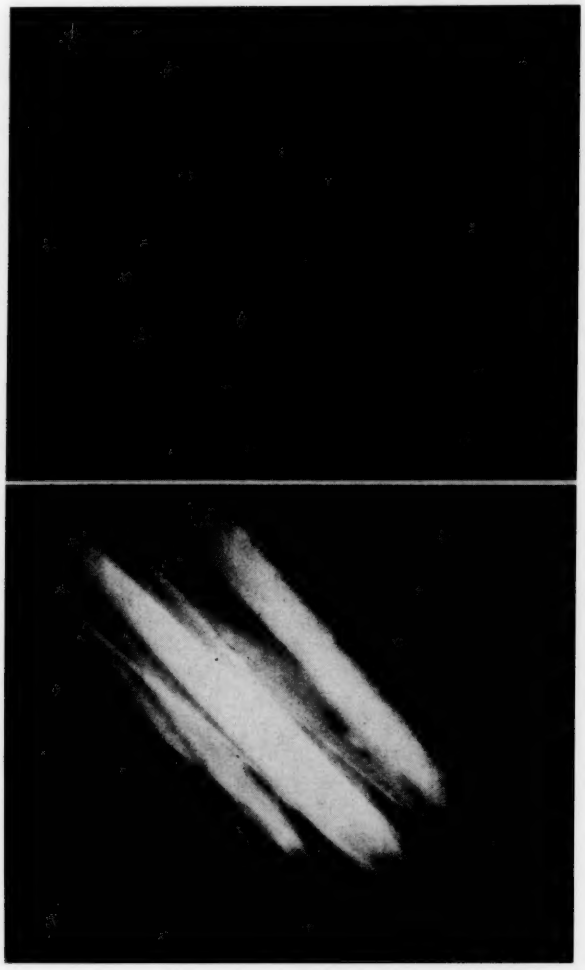

Fig. 2.—Nucleoprotein strands exposed to lupus serum (*lower*) and normal serum (*upper*) and stained with fluorescent anti-γ-globulin. The nucleoprotein selectively acquired γ-globulin from the lupus serum.

have been reported. Particularly pertinent is the well-known study of Callender and Race[1] on the finding of five rare blood group antibodies in a patient with lupus, following transfusion of blood. Antigens of the red cells that are not ordinarily antigenic gave rise to potent antibodies in this patient. The existence of two of these antigens was not known until this case was observed.

VOL. 10 1959

Other points, such as the dramatic and lasting effects of steroids, can be cited in favor of an immunologic mechanism. However, the strongest evidence has appeared recently through a study of the L.E. cell phenomenon. It now appears that the L.E. factor is an antibody to nucleoprotein and that this reaction can be studied and quantitated by classical immunologic procedures. Miescher and Strassle[14] in Switzerland and Seligman[17] in France have carried out a large part of this work. Complement fixation tests with nucleoprotein as antigen, tanned red cell procedures, latex particle agglutination, and fluorescent antibody methods have all demonstrated the interaction between nucleoprotein and L.E. serum factor. Fig. 2 illustrates one of the many ways of demonstrating the interaction of nucleoprotein with the specific protein of lupus serum. The coating of the nucleoprotein is dramatically brought out by secondary staining with fluorescent antibody to γ-globulin. Nucleoprotein exposed to normal serum shows no similar fluorescence.[8,9]

Fig. 3.—Precipitin bands in agar following interaction of DNA and lupus factor. The DNA was layered over the agar and the lupus serum below it. The second tube without any precipitin band was layered with DNA treated with desoxyribonuclease.[3]

Isolated nucleoprotein strands, coated with γ-globulin from lupus sera, are phagocytized by viable leukocytes to give typical L.E. cells. The reaction is completely blocked when the DNA in the nucleoprotein is hydrolyzed by desoxyribonuclease, and it is clear that the DNA is necessary for the interaction. Isolated DNA also gives a precipitin reaction with lupus serum.[3] Fig. 3 illustrates precipitin bands obtained following double diffusion in agar tubes. These were observed only with lupus sera and strongly suggest an antigen-antibody reaction. Desoxyribonuclease completely eliminated the precipitin reaction but ribonuclease or trypsin did not.

Precipitin curves can also be obtained through the interaction of DNA and lupus sera. Complete solubility occurred when excess DNA was added, suggesting antigen-excess solubility. The precipitate could be dissolved readily

after washing through the action of desoxyribonuclease, and the protein from the lupus serum was thus brought into solution in a highly purified state. This protein had all the properties of antibody γ-globulin: the antigenic properties, the electrophoretic and ultracentrifugal properties, and the carbohydrate content. Complement was fixed in the precipitin reaction. Somewhat surprisingly, the DNA precipitating factor did not prove to be the same as the L.E. cell factor although DNA was necessary for the latter interaction. Removal of the DNA precipitate did not lower the L.E. cell activity and the dissolved DNA precipitate had no L.E. cell activity.

It has become apparent, particularly through complement fixation studies, that a large number of different factors, which react with different cell constituents,[15] are present in these sera. These were brought out best by complement fixation procedures with various cell fractions as antigens. In addition to factors reacting with isolated DNA and nucleoprotein, components were found which fixed complement with isolated histone, phosphate extract of nuclei, and various cytoplasmic constituents. These could be differentiated through cross-absorption experiments, susceptibility of the antigens to various enzymes, and differential profiles of reactivity in different lupus sera. Table I illustrates the results with three lupus sera. The first serum fixed complement with DNA but not with histone, while the second serum showed the reverse pattern. Many variations in the profile of reactivity with these antigens were obtained with different sera. Most of the studies were carried out with fractions of human liver and kidney cells. Species specificity was obtained for the cytoplasmic factors but not for the DNA or nucleoprotein reactants.

A study of the mechanism of the L.E. phenomenon thus opened a veritable Pandora's box of autoantibody-like substances in lupus sera of possible potential

TABLE I. SERUM COMPLEMENT FIXATION WITH VARIOUS ANTIGENS[8]

SERUM	L.E. CELL FORMATION	ANTIGEN USED IN COMPLEMENT FIXATION STUDIES	SERUM DILUTION									
			2	4	8	16	32	64	128	256	512	1,024
Tr.	Strong	Nuclei	4	4	4	4	4	4	4	4	2	0
		PO_4 extract	4	4	4	4	4	4	4	4	4	0
		Nucleoprotein	4	4	4	4	4	4	4	4	2	0
		DNA	4	4	4	3	0	0	0	0	0	0
		Histone	0	0	0	0	0	0	0	0	0	0
Fr.	Strong	Nuclei	4	4	4	4	4	4	1	0	0	0
		PO_4 extract	4	4	4	4	4	4	4	4	0	0
		Nucleoprotein	4	4	4	4	4	4	4	2	0	0
		DNA	0	0	0	0	0	0	0	0	0	0
		Histone	4	4	4	4	0	0	0	0	0	0
Me.	Strong	Nuclei	4	4	4	0	0	0	0	0	0	0
		PO_4 extract	4	4	4	4	4	0	0	0	0	0
		Nucleoprotein	4	4	4	4	4	4	0	0	0	0
		DNA	4	4	4	4	2	0	0	0	0	0
		Histone	0	0	0	0	0	0	0	0	0	0

danger to the patient, since they are capable of reacting with the patient's own cell fractions. The question, however, of whether or not these play a role in the manifestations of the disease remains unanswered. Some evidence has been obtained that other immunologic phenomena more analogous to the tuberculin type of reaction may be of significance. A delayed-type skin reaction to the patient's own leukocyte extracts has been observed by Dr. Holman. These results are preliminary, but at least they suggest a fruitful path for future investigation. Regardless of the disease mechanism, it is abundantly clear that profound immunologic alterations are present. The term "immunologic epilepsy" has been applied by Dr. Good to lupus erythematosus because of the extreme hyperreactivity of these patients to immunologic stimuli. Its close relationship to rheumatoid arthritis suggests that similar phenomena may play a role in this disease.

OL.
10
959

The second major point to be considered, which perhaps favors an immunologic abnormality for rheumatoid arthritis, is the characteristic presence of the "rheumatoid factors" in the sera of these patients. These are a group of closely related proteins that are responsible for a wide assortment of serologic tests currently employed in the diagnosis of rheumatoid arthritis; the sensitized sheep cell agglutination test, the Fr. II γ-globulin tanned cell test, the latex fixation test, and several other procedures.[20] It is now clear that all of these reactions are dependent on the use of particulate bodies coated with γ-globulin or antibody and then agglutinated by the rheumatoid factors. Cecil, Nicholls, and Stainsby[2] encountered this reaction when streptococci coated with small amounts of antibody were added to rheumatoid serum. Sheep red blood cells coated with rabbit antibody to the sheep cells are similarly agglutinated as was first observed by Rose and associates.[16] These are two examples, but there are many more, of the accidental discovery of the unique property of rheumatoid arthritis sera to agglutinate particulate bodies coated with γ-globulin. Recently developed modifications of these methods have shown positive serologic reactions for rheumatoid factor in as high as 90 per cent of patients with rheumatoid arthritis compared with less than 5 per cent in control groups.[20]

The accumulated evidence indicates that these factors are not directly involved in a causative manner in the joint lesions, although this has not been entirely ruled out. The association with this disease is a striking one, however, and must eventually be explained. The subject has been well reviewed by Vaughan recently.[19] A number of different laboratories have isolated the rheumatoid factors in the past year and it has become clear that these factors have the chemical, physical, and antigenic properties of a specific type of antibody.[6,11,13] Fig. 4 illustrates the electrophoretic pattern of one preparation of isolated rheumatoid factor. The pattern of the original serum from which this was isolated is also shown. The activity per unit of protein by two of the serologic tests is indicated for both the whole serum and the isolated rheumatoid factor. The active fraction has the mobility of a γ-globulin, which in itself suggests that it may be an antibody. Ultracentrifuge patterns of three purified preparations of rheumatoid factor are particularly characteristic. They show one component with a sedimentation coefficient of approximately 19S and a molecular weight

close to one million. Antibodies such as the isoagglutinins and the cold agglutinins have identical physical properties. The rheumatoid factor is rich in carbohydrate—also a characteristic of antibodies of this class. Table II shows data on the various carbohydrate constituents and illustrates the similarity to normal 19S γ-globulin, which consists of multiple known antibodies. Also, in antigenic properties, the isolated rheumatoid factors are indistinguishable from known antibodies. They differ only in their specific serologic properties. Finally, antibodies of the high molecular weight class are very susceptible to sulfhydryl reagents which break down these macromolecules through cleavage of disulfide bonds. Similarly, the rheumatoid factors are dissociated by these reagents with complete loss of serologic properties.

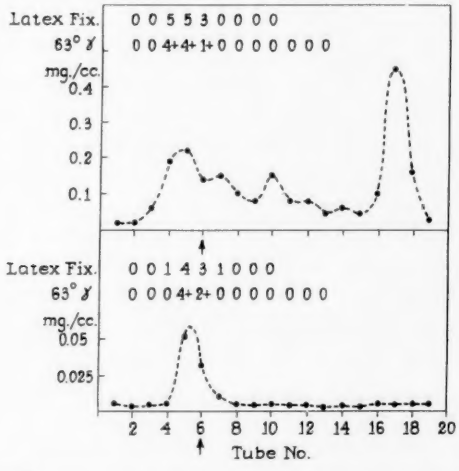

Fig. 4.—Zone electrophoretic patterns of isolated rheumatoid factor and of the original serum. The active fractions migrate as γ-globulins.[11]

TABLE II. CARBOHYDRATE CONTENT OF SEVERAL PREPARATIONS OF ISOLATED RHEUMATOID FACTOR[11]*

PROTEIN	N (%)	HEXOSE (%)	HEXOSAMINE (%)	SIALIC ACID (%)	TOTAL CARBOHYDRATE (%)	HEXOSAMINE/HEXOSE (%)
Normal γ-globulin (7S)	15.64	1.22	1.14	0.22	2.58	0.94
Normal γ-globulin (19S)	14.47	5.20	2.9	1.70	9.80	0.55
Rheumatoid factor preparation II	14.54	5.40	2.9	1.80	10.10	0.55
Rheumatoid factor preparation IV		5.3	2.0	1.70		
Rheumatoid factor preparation V		5.1				

*Previous results for normal 7S and 19S γ-globulin are also indicated.

Observations of this type strongly suggest that these rheumatoid factors represent a group of closely related antibodies. The true antigen involved in their production has not been clearly defined although a certain amount of evidence suggests that they, too, may be autoantibodies made against ordinary

low molecular weight γ-globulin. They combine specifically with γ-globulin, particularly when it coats particles, and not with any other protein of a large number thus far studied. They combine with the patient's own γ-globulin and circulate as a complex. All of the serologic tests for rheumatoid factor depend on this specific interaction with γ-globulin. Fig. 5 illustrates schematically the equilibrium between rheumatoid factor and ordinary γ-globulin. It is a reversible process and both the complex and the isolated 19S rheumatoid factor are active in the serologic reactions. The question of whether or not this represents the union of antigen and antibody to form an antigen-antibody complex is one which intrigues everyone in the field. The answer is not yet available. Certainly the evidence that the rheumatoid factors are autoantibodies is not as good for the lupus factors but it is at least suggestive.

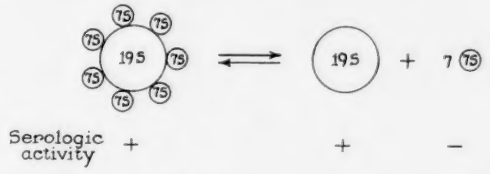

Fig. 5.—Diagrammatic representation of the equilibrium between 19S rheumatoid factor and ordinary 7S γ-globulin. In the body the rheumatoid factor exists as the complex.

The possibility that the rheumatoid factors are antibodies perhaps analogous to the Wassermann antibodies in syphilis should be considered. Here the stimulus of the spirochete apparently produces an autoantibody that in many ways resembles the rheumatoid factor. However, the evidence against the primary role of an infectious agent in rheumatoid arthritis is considerable but certainly not conclusive. Recently the older observations of a strong genetic factor in this disease have been amply confirmed. One family has been observed in which 6 siblings developed rheumatoid arthritis. These siblings varied considerably in age, and the time of onset of the disease in different members was as far as 40 years apart. The use of the serologic tests for rheumatoid factor has aided considerably in carrying out such genetic studies. Positive serologic reactions in asymptomatic relatives were first described by Ziff and co-workers[21] and represent one of the real developments in the field. This has been confirmed by Lawrence and Ball[12] in England, and in our own laboratory. Fig. 6 shows the pedigree of a child with classical juvenile rheumatoid arthritis studied by Dr. Fudenberg in our laboratory. Although they were asymptomatic, both the mother and maternal grandmother had positive serologic tests comparable to those in the patient. It is difficult to postulate an infectious agent as the cause of the rheumatoid factor with such a genetic distribution. Even an agent resembling the Bittner mammary carcinoma virus would be an unlikely possibility. Positive serologic tests have also been encountered in the paternal branch of these families, thus excluding direct passage from mother to offspring.

The final point in favor of an immunologic basis for this disease stems from some preliminary studies on patients with agammaglobulinemia. This disease is characterized by the complete absence of antibodies in the serum and the patients

suffer from continued severe infections. Their immune mechanisms to resist these infections are profoundly altered. Many studies have been carried out on these patients, and there remains no question that this disease is the example par excellence of a basic immunologic alteration. Recently, Dr. Fudenberg and Dr. German[5] have obtained preliminary evidence that may link this disorder with rheumatoid arthritis. Four families of patients with acquired agammaglobulinemia have been encountered in which one or both parents showed the presence of rheumatoid factor, usually without arthritis, detected by several of the serologic tests for rheumatoid factor. In addition, two families have been observed in which lupus erythematosus was found in relatives of the patients with agammaglobulinemia. Both an arthritis resembling rheumatoid arthritis and lupus erythematosus are known to be present in a high proportion of patients with

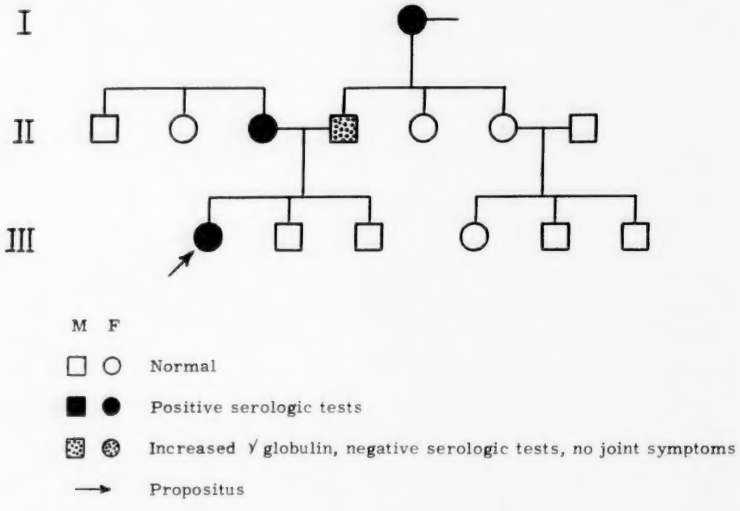

Fig. 6.—Genetic chart of a child with juvenile rheumatoid arthritis. The mother and grandmother showed positive serologic tests without significant joint changes.

agammaglobulinemia. This was first described by Janeway and associates[10] several years ago. The explanation usually offered for this association, however, has been that the arthritis probably resulted from the multitude of infections suffered by the patients with agammaglobulinemia. Now, with the evidence for rheumatoid factor and lupus in relatives, an alternative hypothesis becomes possible—that these diseases are closely related and represent different manifestations of profound immunologic alterations. The linkage on a genetic basis represents the key point involved and requires extensive confirmation in a large series of cases. If this should be forthcoming, strong evidence would be at hand for an altered immune mechanism in rheumatoid arthritis. At present it would appear that immunologic principles beyond our conception are involved. A better understanding of basic immunology and the phenomena of transplantation immunity and tolerance will undoubtedly be required for elucidating these relationships.

In conclusion, it should be emphasized that despite the obvious enthusiasm permeating this discussion, the evidence that rheumatoid arthritis is an immunologic disorder is primarily indirect and is not yet conclusive. Genetic relationships of the type described are very difficult to establish on a firm statistical basis and all the points cited are, in the final analysis, only suggestive. They are suggestive enough, however, to stimulate much further work in this area.

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FUTURE LINES OF RESEARCH ON RHEUMATOID ARTHRITIS

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IN HIS admirable survey of the historical and clinical aspects of rheumatoid arthritis, Dr. Short has pointed out several times that it is most important for clinicians interested in this disease to remain alive to new developments in closely adjacent clinical fields, such as those of rheumatic fever, gout, psoriasis, and ulcerative colitis, in view of the possibility that any news from these quarters may have bearing on the problem of rheumatoid arthritis. His implication is that although these are clinically recognizable as quite different diseases, analogous mechanisms may be involved in parts of them.

This is to be the central theme of my paper, and I intend to emphasize the importance of keeping an eye on analogous situations in neighboring fields in a rather large area of experimental medicine and pathology. To do this, I must run the risk of presenting a rather disjointed lecture, made up of odd-sized parts laid side to side but not quite fitting together.

What I hope to show is that when we begin to examine the pathogenesis of rheumatoid arthritis, we find ourselves quickly and sometimes surprisingly diverted to the study of other diseases—related ones at first, and then quite unrelated ones—or to the investigation of what we hope to be experimental models in animals, which lead out in what soon appears to be all directions. In experimental pathology, as we shall see, one thing leads to another, and there are a great many inviting garden paths.

My point will be that we are limited to an uncomfortably narrow area if we attempt only the direct, frontal, or precise approaches to rheumatoid arthritis as such. We can go only a certain distance before our information and instruments become inadequate for the task, and we are then required to look for new clues or openings in adjacent areas, and then, having studied these analogous situations, to move still further afield. The problems raised by rheumatoid arthritis extend across interdisciplinary lines into an extraordinarily broad field of biology, and answers to the important questions about this disease are less likely to be obtained locally than they are somewhere at the far periphery.

I shall begin with the local dilemma of the joint, in rheumatoid arthritis proper, and finish with a consideration of the normal human placenta, which, in my opinion, shares certain problems with the arthritic joint, and in between, more or less connected together, I shall deal with certain immunologic phenomena that form the links between these distant topics.

OL.
10
959

RHEUMATOID ARTHRITIS

As Dr. Short has indicated, there is a fair degree of agreement among clinical authorities as to *what* rheumatoid arthritis is, or how it is defined—apart from a certain amount of doctrinal dispute, into which I propose not to enter, about the propriety of including such things as psoriatic arthritis or the arthritis of patients with ulcerative colitis or with agammaglobulinemia. The biochemical nature of some of the connective tissue elements involved in the disease is beginning to be better understood, as Dr. Dorfman has shown us, and parenthetically someone should acknowledge, sometime, the considerable debt we owe for our present knowledge of tissue polysaccharide chemistry to work coming from laboratories originally concerned with rheumatic diseases, like Dr. Dorfman's. Dr. Kulka has convinced us of the existence of rheumatoid arthritis as a pathologic entity, and he suggests, on good grounds, that an abnormality in the reactivity of terminal blood vessels may have much to do with the initiating mechanism of tissue damage in the joints. Finally, Dr. Kunkel has presented the evidence for hypersensitivity as the determining event which probably underlies the pathogenesis of rheumatoid arthritis. He has also summarized the recent evidence for a relationship between this disease and disseminated lupus, and further, for the genetic determination of both conditions. I am not as sure as Dr. Kunkel is that the demonstration of genetic determinants necessarily rules out an infectious agent in arthritis, since it seems to me quite possible that a defect in resistance to some universally distributed agent—L-forms, for example, or nonhemolytic streptococci, or some virus or other—could as well be inherited as is the tendency to develop arthritis. I agree with him, however, that infection seems less and less likely, as generation after generation of bacteriologists rise to the problem and fall again.

It seems to me that if we set the possibility of an infectious agent to one side, as an unpromising approach to the arthritis problem, we have abandoned almost the only direct approach there is to the problem. Many investigators are loath to do this, and commendable efforts are being made in certain laboratories to grow something from the joint fluid or tissues of arthritic joints. Certainly nothing could be more direct or convincing than the isolation of a pathogenic agent from the involved tissues, and perhaps something will come of this. But Dr. Kunkel doubts it, and so do I, and in this circumstance what comes next?

Here is where we must begin to move afield. Suppose we consider, for operational purposes, that the rheumatoid factor has something to do with the pathogenesis of arthritis. This is an antibody against gamma-globulin, or, if you will, an anti-antibody, and it exists in the circulating blood attached to its antigen. I am not certain how one could possibly go about showing that an antigen-antibody complex of this kind can be damaging to the joints in patients with rheumatoid arthritis, but an elegant experimental model exists for studying this sort of thing.

SERUM SICKNESS

Serum sickness is a syndrome in which acute polyarthritis, angiitis, and glomerulonephritis occur as systemic reactions to a foreign protein antigen.

There are differences in intensity and pathologic detail from the joint and blood vessel lesions of rheumatoid arthritis, and it would be most unwise to set them side by side as manifestations of precisely the same thing, but still they may be related to each other. At any rate, it would seem in the best interests of arthritis for us to know as much as possible about the mechanisms involved in serum sickness.

Thanks to the recent work of Dixon and co-workers,[4] Germuth,[8] and others, it is now known that the vascular lesions of serum sickness are associated with the local deposition, in the walls of the involved blood vessels, of antigen-antibody complex. It is not understood why such complexes should be irritating to vascular tissue; the possibility has been suggested that proteolytic enzymes are released or activated at the site of deposition and that proteolysis leads to damage of the tissue. Good evidence for or against the notion is not available, but we seem to have been presented with an excellent model with which to explore the matter more deeply. One of the cardinal lesions of serum sickness is acute glomerulonephritis, and McCluskey, Benacerraf, and Potter[13] have recently shown that this lesion can be reproduced in mice within 36 hours or less after an intravenous injection of soluble antigen-antibody complex. In a sense, then, this model for the experimental production of glomerulonephritis in mice can be regarded as one of the currently available approaches to the problem of rheumatoid arthritis.

It is now known that antigen-antibody complexes are removed from the blood stream in a curious fashion, and there are probably variations in the site of uptake depending on the size of the complex and the nature of the antigen. In classical serum disease—for example, the type produced by a massive injection of foreign gamma-globulin—the arteries of the heart and stomach and the glomerular capillaries show the greatest uptake and the most damage. In addition to the blood vessels, the reticuloendothelial cells engulf large amounts of antigen-antibody complex, although they do not seem to be damaged by doing so. It has been claimed that synovial cells can, under certain circumstances, assume the properties of reticuloendothelial cells and undertake the phagocytosis of circulating particulate material. Conceivably, the trouble in rheumatoid arthritis joints might be that the complex of rheumatoid factor and its globulin antigen have been selectively picked up by local vessels, or synovial cells. But this sort of speculation is quite fruitless and can lead nowhere until we know much more than we do about the mechanisms of tissue damage in serum sickness, and the factors which influence the uptake in various tissues of antigen-antibody complexes.

Also, it should be added, any such explanation for the joint lesions of rheumatoid arthritis will create real discomfort in pediatric circles where numbers of children with agammaglobulinemia and a syndrome indistinguishable from rheumatoid arthritis are being studied.[9] To the pediatricians concerned, anything remotely resembling serum sickness would be an impossibility in these children, since they can't make antibody at all. If the rheumatoid factor is involved in the pathogenesis of classical rheumatoid arthritis, it is difficult to see how the same mechanism can account for the arthritis of agammaglobulinemia, unless the

children with this disease possess a more subtle, cellular form of the same factor, analogous to whatever the mechanism is which permits them to have the delayed-type reactions of bacterial allergy.

AUTOANTIBODIES

Apart from the rheumatoid factor and the possibility it has raised of invoking something analogous to serum sickness in accounting for arthritis, there is another immunologic abnormality with rather larger implications. This is the L.E. factor, an antibody directed against DNA or combinations of DNA with other nuclear materials. As Dr. Kunkel showed us, this is demonstrable in over 20 per cent of patients with rheumatoid arthritis, and it constitutes part of the evidence for a close relationship between this disease and disseminated lupus erythematosus.

OL.
10
959

The L.E. factor is, par excellence, an autoantibody. Whether or not it is actually responsible for the various lesions of lupus is not clear. According to some, this is theoretically unlikely, since DNA is present only in sites inaccessible to antibody; but, according to others, there are ample opportunities in the normal breakdown of replaceable cells, notably the lymphocytes, for the L.E. factor to form complexes with its antigen or antigens. The point remains unsettled, and some clarification may be gained by considering other circumstances in which autoimmune mechanisms are known to be involved in tissue destruction and death.

The best of these is the experimental disease known as allergic encephalitis, which is produced by immunizing animals against their own or other animals' brain tissue. This was discovered some 25 years ago by Dr. Rivers,[19] and may turn out eventually to have been as significant a contribution to the arthritis problem as anything else. This was the first unequivocal demonstration of a disease state produced by an immune response within an animal, leading to the selective and specific destruction of one kind of the animal's own tissue by his own antibody. Later, it was found by Kabat and Wolf[10] and Morgan[15] that the same condition can be produced with facility and reproducibility by combining brain antigen with Freund's adjuvant mixture.

The disease has been produced in monkeys, rabbits, dogs, cats, rats, mice, and other laboratory animals.[16,17] The microscopic lesions in the brain show patchy areas of demyelination reminiscent of the lesions of multiple sclerosis in humans and inflammatory involvement of the veins and venules, with infiltration in and around the vessel walls by dense masses of mononuclear cells, many of which appear to be plasma cells.

Waksman[31] has suggested that the type of circulation of blood through the venules and small veins may be important in determining where lesions occur. If the flow of blood is sufficiently slow, and the arrangement of venules sufficiently elaborate, mononuclear cells in the blood can become attached to the vessel walls, migrate through, and form the granulomatous vascular lesions which characterize allergic encephalitis. He suggests that the surface charge of the leukocytes and that of the vessel walls may be of importance in determining the particular areas into which cells penetrate. But it also seems possible that the force that attracts

the mononuclear cells to these particular veins may be the antigen, just across the wall, in the white matter of the brain, and the cells may be attracted because they are already forming antibody against brain antigen. The situation may be analogous to that shown earlier with isolated lymph node cells from animals immunized against certain bacteria; when placed in a suspension of the same microorganisms, the surface of the cells become coated with agglutinated masses of bacteria.[18] Here, in the brain, the same thing may be going on in reverse, with masses of antibody-forming cells sticking to the surface of a very large antigenic mass.

It should be said at once that, although there is no reasonable doubt as to the immunologic basis of this disease, nor as to it exquisite specificity for the white matter of the brain, very little is known about the nature of the autoantibody involved, and nothing is known about how the tissue is damaged. A complement-fixing antibody occurs in the serum of rabbits, dogs, and several other species after immunization with brain adjuvant mixtures,[16,24] but no one has yet succeeded in transferring the disease from one animal to another by injecting serum, even in heroic amounts. Recently, Paterson[17] reported successful transfer of paralytic disease in rats by the intravenous injection of lymph node cells from immunized animals, suggesting the possibility that this disease involves the delayed, or tuberculin, type of allergy (which can be transferred with cells but not with serum). Waksman and Morrison,[30] by the way, have shown that animals developing allergic encephalitis show skin reactions of the delayed type when injected intradermally with brain extract.

Other organs have been shown to be vulnerable to autoimmune destruction by the same techniques used in allergic encephalitis. Aspermatogenesis and destruction of testicular cells occurs in guinea pigs after immunization with testis extract combined with Freund's adjuvants.[7] The adrenal gland, pancreas, and uveal tract of the eye[3,16] are reported to react similarly, after appropriate immunization.

One of the most striking examples, and one which will direct our attention back to lupus and arthritis, is allergic thyroiditis. Witebsky and Rose[32] have shown that immunization with thyroid extract and Freund's adjuvants leads to acute thyroiditis, with circulating antibodies which react with thyroglobulin in extremely high titer. Since this work, it has been demonstrated that Hashimoto's disease, a form of thyroiditis in human beings, is also associated with the presence of antithyroid antibodies in the patient's serum.[20] Now it appears that this kind of autoantibody may represent, in some patients, a manifestation of lupus erythematosus. I have recently been shown, by other clinicians, material from 2 patients with Hashimoto's disease, who also had positive L.E. reactions, and Vazquez[29] has demonstrated antinuclear antibody in the serum of patients originally presumed to have only Hashimoto's disease.

Thus, we now have quite good evidence for the existence of autoimmune disease involving several different organs in experimental animals, and quite good evidence for an autoimmune process in thyroiditis in the human. With all this, the position for regarding autoantibodies as important factors in lupus erythematosus seems a stronger one. From here to a similar view of rheumatoid arthritis, with its rheumatoid factor, or with some other antibody against some as yet undetected tissue antigen, would require no great leap of the imagination.

HOMOTRANSPLANTATION IMMUNITY

What is needed, at this point, is more information about the actual mechanisms concerned in autoimmune disease and, in particular, about the pathologic events involved in this kind of tissue damage. For this, it may be helpful to turn our attention to another experimental model in which the immunologic destruction of a predictable area of living tissue can be brought about, so to speak, before our very eyes. This is the phenomenon of homotransplantation immunity, best exemplified by the rejection of a skin graft.

Consider the situation of a homograft of skin, from one albino rabbit to another, on the fifth day after transplantation. The tissue is at this stage well vascularized, healthy in appearance, and, for all intents and purposes, part of the recipient rabbit's own living tissues. If examined histologically on this day, there would be little to choose between this piece of skin and an autograft of the same rabbit done at the same time. However, within the next day or so, the homograft will become infiltrated by large numbers of lymphocytes and plasma cells, densely concentrated in the immediate vicinity of small blood vessels. Small thrombi will occur in capillaries and venules, followed by petechial hemorrhages which eventually become confluent, and, on the eighth or ninth day, the homograft will undergo rejection.

If now, after rejection, the same animal is grafted a second time with skin from the same donor, accelerated rejection occurs and the skin is destroyed on the third or fourth day.

This, as Medawar, Billingham, and their colleagues have shown, is an immunologic phenomenon, and it represents one of the most highly specific and selective forms of hypersensitivity.[14] It can be transferred from one animal to another by means of leukocytes and is associated with skin reactivity of the delayed, or tuberculin, type. It provides an experimental model for studying in detail a kind of artificial autoimmune state in which an animal first accepts and incorporates a living tissue into his own, then recognizes it as containing foreign antigenic material, and finally rejects it by actively destroying it in its entirety.

Several years ago, Medawar and his associates discovered the phenomenon known as homograft "tolerance," which has since opened up several new approaches to the study of autoimmune reactions. They found that when living cells from one mouse are injected into a newborn mouse of another line, the newborn animal is misled into regarding the injected cell line as his own. When fully grown, such a mouse can be grafted with skin or other tissues from the other line, and will accept them permanently as though they were autografts.

This observation, which seemed to hold promise for future new ways of bringing about permanent retention of homografts, soon led to an ancillary finding with quite the opposite implications—the so-called "runting syndrome"[2]—which has suggested an entirely new approach to the problem of autoimmunity and tissue destruction.

The runting syndrome is brought about in the following manner: Spleen or lymph node cells from inbred adult mice of one line, say Ajax, are injected in large numbers into newborn mice of another line, say C57. When this is done,

two things begin to happen. The recipient mouse, C57, becomes "tolerant" to the injected Ajax cells, and allows them to proliferate, distribute themselves throughout his tissues, and survive. But, the second event is that the injected cells, having come from mature Ajax mice, are themselves not tolerant, and begin to form antibodies to the C57 tissue antigens in which they find themselves. The newborn mouse, in this situation, cannot survive; he becomes profoundly anemic, develops extensive lesions of necrosis in his liver and other organs, fails to grow, and dies within two weeks or so after birth. Here, instead of the host rejecting a graft, the graft has rejected the host.

It has recently been learned in our laboratory that runting can be prevented if the newborn mouse receives an injection of adult, isologous spleen cells at the same time as the homologous spleen cells, presumably indicating that the isologous cells have converted the newborn, temporarily at least, into an immunologically adult animal. We have also prevented runting by immunizing pregnant mice with the homologous cells; litters from such mothers do not undergo runting when injected with homologous spleen cells. Furthermore, serum from adult mice immunized against homologous cells will confer passive protection against runting.[23]

This area of immunology, or immunopathology, seems alive with possibilities for the study of diseases presumed to be associated with autoantibodies. If we can look far enough along these approaches, we may find out new things about the ways in which foreign antibody-forming cells become established in individuals, and the ways in which the activity of such cells can be cancelled without jeopardy to the host.

Whether or not this experimental situation has anything to do with the rheumatoid factor, the L.E. factor, or any of the known autoimmune diseases, seems to me almost beside the point, in view of the intrinsic interest in tolerance and runting which has been developed in many laboratories across the world, regardless of its implications for other disease states. Nevertheless, I suggest that those of us who are primarily interested in the pathogenesis of rheumatoid arthritis and lupus would do well to keep a sharp eye on anything new that turns up in the homotransplantation problem, and particularly in the runting syndrome.

The runting syndrome contains, by the way, the implication that any defect in the placenta which might permit maternal reticuloendothelial cells to take up residence in the fetus might lead to serious immunologic difficulties later in life, in a hybrid species. Apart from this, there are other reasons for us to be interested in pregnancy, which I should like to introduce as the next digression in this lecture.

It is a famous fact that rheumatoid arthritis often seems to undergo remission during pregnancy, a state of affairs attributed in some quarters to cortisone.

Another, less famous but equally interesting, fact about pregnancy is that various other inflammatory reactions involving hypersensitivity seem to come under some dampening influence. Skin reactions to bacterial antigens, such as tuberculin, are said to become milder, various allergies ameliorate, and it is even claimed that skin homografts persist for longer than survival periods.

VOL.
10
1959

THE FETAL PLACENTA

The most remarkable instance of immunologic apathy in pregnancy seems to me to be the placenta itself. The fetal placenta, in any hybrid species such as ourselves, is in the biologic position of a homograft. The great mass of the placenta, with its branching stalks of chorionic villi covered by syncytial trophoblast, is actually a very large vascular compartment lined by the cells of one individual—the fetus—through which must circulate the blood of an immunologically distinct individual—the mother. If we knew how this sort of homograft manages to survive for 9 months or so, instead of being rejected after 7 or 8 days as would be the case with other kinds of homografts, we would probably know something quite useful for our understanding of autoimmune phenomena in general. Also, parenthetically, we might have a better understanding of some of the pathologic events which interrupt pregnancy, such as eclampsia, premature separation of the placenta, and even habitual abortion.

There are, of course, several ways to explain away this dilemma. One is to take the stand that the fetal trophoblast is forever so immunologically immature as to be anonymous throughout all of pregnancy. This may be the case, but if it is it would imply that the trophoblast is unique among fetal cells, since sooner or later at some time during pregnancy and before parturition, all other fetal cells become antigenically mature. In the ninth month of gestation fetal tissues in general are recognizable as homografts and are rejected by adult recipients, but the fetal placenta succeeds somehow in persisting.

It occurred to us that perhaps the placenta has a way of continually desensitizing the mother against itself by steadily releasing its own cells into the maternal circulation. This was suggested, initially, by the frequent reports by pathologists, beginning with Schmorl,[22] of the finding of trophoblast fragments in the capillaries of the mother's lung in deaths from various causes during pregnancy, and especially in deaths from eclampsia.

Billingham and Brent[1] showed several years ago that the survival of skin homografts in mice could be considerably prolonged if the recipients of the graft were injected by vein, beforehand, with large numbers of viable cells from the donor of the graft. It is a reasonable guess that some kind of desensitization, perhaps simply due to flooding of the host with a vast excess of viable antigenic cells, is responsible for this prolongation of graft survival.

Recently, we have learned that an analogous process is going on during most of pregnancy.[28] We have sampled the uterine vein blood at various stages of pregnancy from the twelfth week onward, and have consistently found that unmistakable syncytial trophoblasts are present in the maternal blood.

These cells are obviously so large that they would inevitably be stopped by the pulmonary capillary circulation and, in view of the fact that approximately one such cell is contained in each cubic centimeter of blood returning from the placenta, some mechanism must exist for their destruction. Otherwise, it is evident that the lungs would be virtually replaced by trophoblast after a few weeks of pregnancy. A possible mechanism for the lysis of trophoblasts is suggested by our finding that they are extremely vulnerable to the action of trypsin

and also plasmin. Within a few minutes after exposure of intact, viable syncytial trophoblasts to crystalline trypsin, in concentration as low as 1 mcg. per cubic centimeter, the cells become vacuolated, their membranes rupture, and they disintegrate completely. This does not occur with any other known type of cell, and appears to be a special property, or vulnerability, of the trophoblast. Perhaps, as these cells are released into the maternal blood and lodge as microemboli in the mother's lungs, plasma proteolytic enzymes become activated and destroy them. And perhaps, if this is indeed the case, abnormalities in the balance of protease and substrate may be implicated in some of the accidents of pregnancy. This remains to be determined, but the possibility exists that here, at the far periphery, we may be dealing with mechanisms involved in the regulation or suppression of autoimmune reactions in general, and with events related to those which occur in rheumatoid arthritis. At any rate, it seems worth while and perhaps of importance to keep an eye on this adjacent field. One attractive opening is the recently reported observation[21] that pregnant women do seem to become immunized to the cellular antigens of other human beings, as judged by the frequent occurrence of agglutinins for human leukocytes in women after 5 or 6 pregnancies. Perhaps this is due to repeated immunization with trophoblast, and the sharing of common antigens between trophoblasts and leukocytes. It is, in any event, worth looking into.

VOL
10
195

EFFECT OF PAPAIN

I should mention one other approach to the arthritis problem which turned up in our laboratory while we were attempting to learn something about the origin of fibrinoid. As Dr. Dorfman has already mentioned, we formed the view that the intravascular fibrinoid deposits in the generalized Shwartzman reaction might be due to interaction between fibrinogen and an acidic polysaccharide of large molecular size, with precipitation of fibrinogen as an insoluble mass.[25,26] To explore this further, we tried to manipulate the amount of available fibrinogen in the blood by injecting a variety of proteolytic enzymes, and by good fortune happened on papain. Papain had no effect relevant to the fibrinogen problem, but did something else which led us straight down a new garden path, away from the Shwartzman reaction, and, I suspect, closer to problems of rheumatoid arthritis than we would have predicted at the outset.

In brief, we found that when a normal rabbit is given an intravenous injection of papain,[11,12,27] the ears collapse, partially at 4 hours and completely at 12 hours. This curious cosmetic effect is due to the loss of cartilage matrix. The same change, with depletion of the basophilic component of cartilage, occurs in other cartilaginous tissues in all parts of the body. As depletion of the basophilic component of cartilage occurs, chondroitin sulfate disappears from the cartilage and appears in the rabbit's blood. Evidently, what papain has done is to uncouple chondroitin sulfate from whatever the protein is that binds it in cartilage, and when this happens the structural integrity and rigidity of cartilage are lost.

The mobility of chondroitin sulfate away from cartilage is hardly less striking than its resynthesis, or redeposition. Within 2 or 3 days the rabbit's ears are up again, and the cartilage begins to resume its normal histologic appearance.

Cortisone prevents the reconstitution of cartilage, and therefore maintains the ears in a state of permanent collapse, presumably by preventing, as it is supposed to do, the synthesis of sulfated mucopolysaccharide. These effects of papain and cortisone offer unexpected approaches for study of the pathophysiology of joint tissues.

EFFECT OF VITAMIN A

In closing, I should like to present one final illustration of the biologic distance that can be spanned within the problem of arthritis, and the distance from which different biologic phenomena can be related to each other. Fell and Mellanby,[5] some years ago, showed that the addition of vitamin A to embryonic bone cultures caused a depletion of basophilia, and of chondroitin sulfate, from the growing cartilage. Recently, Miss Fell and I[6] discovered that this action of vitamin A could be duplicated by the addition of crystalline papain protease to the plasma on which embryonic bones were cultivated. Having found this, we felt duty bound to turn the thing around, and we fed vitamin A by stomach tube, in large doses, to young rabbits. Within 36 hours, the ears collapsed, basophilia and metachromasia disappeared from the cartilage matrix, and chondroitin sulfate appeared in the blood, indicating that something analogous to the action of papain, conceivably the activation of a tissue protease by vitamin A in cartilage, had occurred.

OL.
10
959

CONCLUSION

I seem to have suggested that the problem of rheumatoid arthritis may include not only such immediately related clinical problems as disseminated lupus erythematosus and rheumatic fever, but also such more distant phenomena as serum sickness, allergic encephalomyelitis, thyroiditis, homograft rejection, immunologic tolerance, the runting syndrome, the relation of the fetal placenta and the maternal host, the effects of papain, and those of vitamin A. I should now make it clear that none of these are seriously proposed as answers to the rheumatoid arthritis problem; rather, they represent illustrations of the diversity of fields in which questions can be asked which are comparable to questions now being raised concerning rheumatoid arthritis. I am sure that my colleagues on the panel could construct a much larger list of problems in fields not mentioned in this lecture. The point to be made is that the future lines of research in rheumatoid arthritis must include areas which now appear to be at the remotest periphery, for it is here that investigation will eventually lead to the most pertinent and meaningful, although at the moment unpredictable, questions.

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VOL. 10 195

THE MEASUREMENT OF SUCCESS IN WEIGHT REDUCTION

An Analysis of Methods and a New Index

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WEIGHT reduction has become a subject of enormous medical and popular interest. Many types of treatment are available and new techniques are constantly being reported; however, the large amount of clinical literature in obesity therapeutics has contained little that can be rigorously evaluated by scientific standards. Many reports have not provided enough data. Others have stated their results using so many different criteria that one program cannot be compared with another. Individual performances in losing weight have been described by use of techniques of measurement which cannot be applied to other patients in the same program or in other programs. In addition, the comparison of total effectiveness among different dietary regimens has often been impossible because no records were given of the performance of *all* the patients exposed to the procedure. Most dietary reports have discussed only the patients who adhered to the program and have not considered those who abandon treatment.

Among the major causes of these difficulties are the absence of a standard definition of "success" in the treatment of obesity and the lack of uniform criteria for measuring dietary accomplishment. This paper will review some of the existing concepts in this field, will analyze the methods by which dietary accomplishment has been measured, and will suggest a new index which can improve some of the existing deficiencies in these techniques.

DEFINITION OF DIETARY SUCCESS

The Target Weight.—Obviously, success in the treatment of obesity cannot be discussed without a definition of obesity itself. This creates an immediate problem. Definitions of obesity have never been precise because the component terms of the definitions are often left undefined. It is clinically useful to state

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that obesity is "excessive body weight chiefly due to abnormal accumulation of fat tissue"[1] but quantitative distinctions are then required regarding "excessive" body weight and "abnormal" accumulation of fat tissue. The problems and methods involved in measuring the latter properties have been presented in detail by Keys and Brozek[2] and Mayer.[3] These papers review existing techniques and indicate that none is generally applicable and available. Useful estimations of body fat can be obtained from (1) skinfold thickness at various sites, (2) teleroentgenographic observations, (3) body density measurements, and (4) body water measurements, but these determinations are generally performed only in research settings. For most clinics, the simple and traditional measurements of weight, height, and age are the primary data. These data are then used with appropriate tables to indicate an "ideal" or "standard" weight whose difference from the initial value will give the surplus weight.

The tables that are used for these purposes have a number of severe limitations, as Keys and Brozek[2] have noted. The "ideal" weight tabulations[4,5] were constructed arbitrarily and their title carries an implication of desirability without specifying its nature. Presumably, the reference is to mortality, although (1) the original data on which the "ideal" weights were based have not been re-evaluated for this feature, (2) the statistical correlations between obesity and mortality have established association but not causation, and (3) decreased "mortality" alone is seldom the goal of most programs of weight reduction. Moreover, the "ideal" weight tables require body classification into types of skeletal frame but do not provide criteria to be used for the classification. Thus, the visual assessment of a body frame as "small, medium, or large" is a gross observation, made with unspecified concepts of bony structure which is often distorted by overlying adiposity.

The most generally used "standard" weight tables emanate from the medico-actuarial investigation of 1912.[6] These data were compiled by pooling life insurance companies' measurements, taken in 1885-1910, of 200,000 men and a somewhat smaller number of women. The heights and weights were recorded with shoes and street clothes, the nearness of a birthday in measuring age was not considered, weights were often estimated rather than actually measured, and no provision was made for sizes of body frame. Despite these deficiencies in their preparation, the tables have correlated well with subsequent revisions[7] and have been widely used for determining standard weights. Since these weights are based only on height, age, and sex, their selection in an individual situation is not influenced by subjective estimations of the physician or patient.

For practical purposes, it is unrealistic to make rigid use of formal tables in planning goals for an overweight patient, since this approach fails to recognize that many attempts at weight reduction are motivated by esthetic, cosmetic, or psychological factors[8] rather than by physiologic concepts or the statistical features upon which the tables are based. These other incentives are often the main reason for dietary attempts and they may play crucial roles in a patient's performance. Their influence is an important feature in the recommendation or evaluation of weight reduction programs.

For many clinical situations, therefore, obesity cannot be defined in a strictly numerical fashion, and decisions in individual cases must be made by the physician as a medical judgment. Inspection and palpation can be used to determine the presence of excessive adiposity. The measurement of height and age will provide data for tables which suggest a weight of statistical desirability. Consideration of the patient's present status, previous dietary performances, and present motivation will help in the estimation of the weight realistically desired. All of these features will enter the considered judgment of the physician as he selects a target weight for a dietary program. For some obese individuals the physician may feel that the anatomic benefits of dieting will not compensate for possible adverse psychic effects and no target weight or diet will be recommended. For most overweight patients, the target weight will be chosen from tabulated values. In some patients, it may be arbitrarily chosen to be more or less than "standard" or "ideal" weights. It may or may not reflect an excess of adipose tissue, and may be chosen only for cosmetic anticipation. However selected, it is a vital factor in any dietary regimen, since the attainment of "success" (as indicated below) will be dependent, in part, on how closely the target weight has been approached.

The Recording of Dietary Results.—The goal of weight-reduction is to get and keep a desired lower weight. This is achieved in two stages: first is the period of "active dieting" during which weight is lost; second is the attempt at long-term maintenance in the reduced state. It is evident that what occurs in the second stage will determine a patient's ultimate "success" and that long-term performance is the most significant evidence of dietary accomplishment. Such long-term data, however, are frequently difficult to evaluate and, with rare exception,[9,10] they are not generally available. Since most dietary reports have given results only for the interval of active weight reduction, the diets can be compared only in this respect. The assessment of long-term results requires separate analytic techniques and the discussion below will apply only for the active weight-reduction period.

For this period, the results of a dietary regimen can be expressed in two ways: (1) an objective criterion of accomplishment is established to evaluate the performance of individual patients; (2) the degree of accomplishment is measured in all of the patients who began the diet. The necessity for checking results in all of the starting patients is evident. Nevertheless, as several workers have commented,[11,13] most publications do not give these data, and tabulate only patients who continued with a dietary procedure and not those who abandoned it. Without such information, it is obviously impossible to compare different dietary programs.

EXISTING METHODS OF EXPRESSING DIETARY "SUCCESS"

A "successful" diet should enable weight loss without undesirable physiologic or psychological effects. These effects are often subtle and their cause is difficult to determine. They create a separate variable[14] whose evaluation in individual patients is often impossible. For simplicity, they will not be considered in the present analysis which will be confined to quantitative aspects

of weight change. Under these conditions, the best measurement of dietary "success" would appear to be the relationship of the patient's initial obese status to the amount of weight lost and the amount of loss that was desired. The time required in the weight reduction process and fidelity of adherence to a prescribed diet are presumably of secondary importance as long as the end result—loss of weight—is achieved. These premises, and those discussed previously, provide the basis for evaluating existing methods of expressing dietary "success."

For the period of active weight reduction, the following numerical data can be conveniently obtained:

W_I = Initial weight
W_T = Target weight
W_E = Weight at end of reduction (i.e., lowest weight achieved)
D = Duration of dieting

From these figures, the following data can be algebraically derived:

$$\text{Surplus or excess weight} = W_S = W_I - W_T$$

$$\text{Relative obesity percentage} = \frac{W_I}{W_T} \times 100$$

$$\text{Weight lost} = W_L = W_I - W_E$$

$$\text{Rate of weight loss} = W_L/D$$

$$\text{Percent of excess weight loss} = \frac{W_L}{W_S} \times 100.$$

These values have been used to establish various standards of accomplishment in dietary programs. The standards are described below, together with an appraisal of their relative merits.

Rate of Weight Loss (W_L/D).—The most commonly used measurement of dietary achievement is the rate of loss in pounds per week or grams per day. This method has numerous deficiencies. The early phases in a period of caloric restriction are generally associated with a rapid fall in weight largely due to loss of tissue water.[15,16] The subsequent weight loss is smaller despite maintenance of caloric deprivation.[2] In other instances the passage of time generally brings an increased intake of food and with it, a decline in the amount of weight lost. Thus, an index which divides total weight loss by the time consumed may give falsely high results if measured after a brief interval of dieting. The values will be relatively low if the rate is measured after longer periods of time. For example, a patient who reduces 20 pounds and abandons a diet after one month has lost an average of 303 grams per day. His rate is higher, but his total accomplishment is less than that of the patient who has lost 15, 10, 8, 7, 8, and 6 pounds in each of 6 consecutive months, for an average over-all rate of 136 grams per day and individual monthly rates of 91 to 227 grams per day.

The use of the rate as a measurement of dietary accomplishment thus exerts a bias in favor of the patient who diets for a brief interval and then quits. It penalizes the patient who continues the program for longer periods of time. In addition to these disadvantages, a "rate" measurement does not consider either the achieved or the desired goal of an individual program.

Performance Index.—This compares the patient's actual rate of weight loss against his anticipated weight loss. The latter can be calculated at the beginning of the program by making a series of assumptions based on the following premises: The basal caloric requirement is determined either from the nomogram tables introduced by Boothby and associates[17] or by converting the oxygen consumption of the metabolism test into calories. Dubois[18] has shown that the oxygen consumption of most individuals in the basal state has the equivalent of 4.8 calories per liter. Thus the BMR test gives a value of O_2 in cubic centimeters per minute which is multiplied by 6.91* to indicate the basal caloric requirement per day. To this basal requirement is added an arbitrary 20 to 50 per cent chosen for the assumed energy needs of the patient. From this total daily caloric requirement, the prescribed calories are subtracted. The remainder is the daily caloric deficit which is converted into an anticipated weekly rate of weight loss by multiplying by a factor of 0.02. The derivation of this factor was shown by Wilder,[19] who first suggested comparing the anticipated weight loss against the actual weight loss. Many years later, Jolliffe and Alpert[20] applied the term "performance index" to this ratio and described its use as a method of measuring dietary accomplishment. Thus,

$$\text{Performance index} = \frac{\text{Actual weight loss}}{\text{Anticipated weight loss}} \times 100.$$

This index may conveniently be used to determine and discuss dietary *adherence* since it indicates how faithfully the patient has observed the prescribed caloric deprivation. However, it does not assess the amount or relative worth of the weight loss. Since it can be applied only to the dieter who continues with a program, it permits falsely high values to be attained by individuals who abandon diets after short periods of time. Moreover, the scientific validity of this index is doubtful because of the many unverifiable assumptions required in calculating the caloric requirement and the anticipated weight loss.

Actual Weight Loss (W_L).—A simple statement of the total amount of lost weight can be used to express individual results. It can also be used for considering the performance of a group of dieters. This is done by tabulating the percentages of patients who achieved certain arbitrary levels of weight loss. A convenient subdivision has been: (1) percentage of patients who gained weight or lost less than 10 pounds; (2) percentage of patients who lost 10-19 pounds; (3) percentage of patients who lost 20 pounds or more. Occasionally a fourth group is added—percentage of patients who lost 40 pounds or more.

This single datum, W_L, does not utilize the patients' initial or surplus weights. For this reason, total results are likely to be superior in groups with very obese patients, since their absolute weight losses will probably be higher. Consequently, this method of expressing accomplishment exerts a bias against the less obese patient. For example, a 20 pound loss may be significant in an individual whose

*Let the O_2 consumption be Y c.c./min. Then

$$Y \frac{\text{c.c.}}{\text{min.}} \times \frac{\text{Liter}}{1{,}000 \text{ c.c.}} \times \frac{60 \text{ min.}}{\text{hr.}} \times \frac{24 \text{ hr.}}{\text{day}} \times \frac{4.8 \text{ cal.}}{\text{Liter}} = Y \times 6.91 \frac{\text{cal.}}{\text{day}}.$$

starting weight was 150 pounds but the same loss has less value if the starting weight was 300 pounds. If a loss of 20 pounds or more is used to represent "success," certain clinical studies might report excellent results with a dietary regimen whose "superiority" is due to the comparatively greater adiposity of the starting population rather than to any intrinsic advantages of the diet program.

Percentage of Excess Weight Lost $\left(\frac{W_L}{W_S} \times 100\right)$.—In any individual performance, it is important to compare the weight loss achieved against the goal which had been sought, and the percentage of excess weight lost attempts to do so. However, the ratio which gives this percentage does not consider the initial weight. A bias is thereby created against the more obese patient. For example, a woman who weighs 140 pounds and loses 20 pounds to a target weight of 120 pounds has eliminated 100 per cent of her excess weight. A 300 pound patient who loses 100 pounds toward a target weight of 150 pounds has performed a more significant dietary accomplishment but is credited with only 67 per cent when judged by per cent of weight loss. The excess weight loss percentage thus has certain utility in assessing individual results but is not adequate for comparisons among different patients.

Weight Loss Compared to Initial Weight.—This technique was introduced by Trulson, Walsh, and Caso,[12] who established the following criteria for "success" in weight reduction:

INITIAL WEIGHT (POUNDS)	MINIMUM WEIGHT LOSS REQUIRED FOR "SUCCESS" (POUNDS)
Less than 150	Over 10
151-175	Over 15
176-200	Over 20
201-225	Over 25
226-250	Over 30
over 251	Over 35

These criteria, although arbitrary and arranged in abrupt divisions, give importance to the role of initial weights in determining dietary accomplishment and are perhaps the most satisfactory of existing indices; however, they do not provide for the effect of surplus weight. This omission may be desirable since it avoids the problem of selecting a target weight, but it creates situations in which patients of identical starting weight, but otherwise grossly different, are judged by the same standard. Thus a man of 175 pounds might have a surplus weight of only 10 pounds while a woman of the same weight might need to lose 50 pounds. If the described criteria are used, the man would be "unsuccessful" if he lost his 10 pounds while the woman would be "successful" if she lost as little as 15 pounds.

A NEW REDUCTION INDEX

As noted previously, none of the existing methods for measuring dietary accomplishment is entirely satisfactory in specific comparisons among individual patients and dietary regimens. Clearly, a desirable index of weight reduction must relate the actual weight loss to both the initial weight and the surplus

weight, and it need not provide for the time in which the loss is accomplished or for the degree of adherence to a diet. The easiest way to get all the desired factors into a single expression would be to modify the per cent of excess weight loss by some factor which compensates for the degree of overweight. Multiplication by the "relative initial obesity" provides this factor. With these considerations, a simple expression can be logically formulated:

$$\text{Reduction index} = \text{Per cent of excess weight lost} \times \text{Relative initial obesity} = \frac{W_L}{W_S} \times \frac{W_I}{W_T} \times 100.$$

This expression provides for all the desired variables. Its terms have been described above, viz., W_I = initial weight, W_T = target weight, W_L = weight lost, W_S = surplus weight. The expression may be rewritten as follows:

$$\text{Reduction index} = W_L \left(\frac{W_I}{W_S\ W_T}\right) \times 100.$$

The term $\left(\frac{W_I}{W_S\ W_T}\right) \times 100$ can be calculated at the beginning of the dietary program and designated as the reduction coefficient, R. C.

Inspection of the terms in this coefficient shows the crucial role of W_T, the target weight. Since its subtraction from the initial weight determines the surplus weight, the target weight directly influences both terms in the denominator of this expression, viz.:

$$\text{R.C.} = \frac{W_I}{W_S\ W_T} \times 100 = \frac{W_I}{(W_I - W_T)W_T} \times 100.$$

The target weight can be selected objectively for an individual patient by using standard weight tables or it can be chosen with the subjective elements introduced by "ideal weight" tables or by arbitrary allowance for psychological and cosmetic goals. The most uniform comparisons of different patients would be obtained by choosing target weights only from standard weight tables. In practice this is impossible, and the physician will often make arbitrary choices in selected cases.

The range of variation in R.C. which these arbitrary choices can produce is shown in the following algebraic considerations: Let K = the degree of relative obesity, $\frac{W_I}{W_T}$. Then in any individual patient, K will vary inversely with the choice of W_T. The expression for R.C. may be written:

$$\text{R.C.} = \frac{W_I}{(W_I - W_T)W_T} \times 100 = \frac{W_I \times 100}{\left(W_I - \frac{W_I}{K}\right)\left(\frac{W_I}{K}\right)} = \frac{W_I \times 100}{\left(\frac{W_I K - W_I}{K}\right)\left(\frac{W_I}{K}\right)} = \left(\frac{K^2}{K-1}\right)\left(\frac{100}{W_I}\right).$$

For a fixed value of W_I, this expression will have its largest values as K approaches unity, i.e., when the target weight is very close to the initial weight. By use of methods of the calculus, it can be shown that the expression has its minimum value, R.C. = $400/W_I$, when K = 2, i.e., when the patient is 100 per cent overweight.

Examples of some of the variations in R.C. produced by different target weights are shown in Table I. This table indicates that arbitrary choices of target weight for most clinical purposes will create a range of variation for the reduction coefficient from $400/W_I$ to $720/W_I$. The upper number, $720/W_I$, will be exceeded only if the patient is *less* than 20 per cent overweight. Since patients in the latter category are not generally regarded as significantly obese, they will rarely appear in most studies of "serious" dieting. Although a range of $400/W_I$ to $720/W_I$ permits considerable arbitrary variation in the reduction coefficient, its practical use will demonstrate that this variation is not excessive and that it has internal consistencies.

TABLE I. RANGE OF VARIATION IN REDUCTION COEFFICIENT DUE TO DIFFERENT CHOICES OF TARGET WEIGHT

$\frac{W_I}{W_T} = K$	PERCENTAGE OVERWEIGHT	$\frac{K^2}{K-1}$	REDUCTION COEFFICIENT
1.05	5	22.1	$2,210/W_I$
1.1	10	12.1	$1,210/W_I$
1.2	20	7.2	$720/W_I$
1.25	25	6.2	$620/W_I$
1.3	30	5.6	$560/W_I$
1.4	40	4.9	$490/W_I$
1.5	50	4.5	$450/W_I$
1.75	75	4.0	$400/W_I$
2.0	100	4.0	$400/W_I$
2.5	150	4.2	$420/W_I$
3.0	200	4.5	$450/W_I$
3.5	250	4.9	$490/W_I$
4.0	300	5.3	$530/W_I$

A more concrete illustration of this point is provided in Fig. 1, which shows actual values of the reduction coefficient in patients with different initial weights at arbitrarily chosen values for target weight and for percentage of excess weight. This chart indicates a number of pertinent points:

1. With higher initial weights, the available range of R.C. becomes smaller. For example, at an initial weight of 200 pounds, R.C. will range from 2.05 to 3.1 as the target weight ranges from 110 to 160 pounds. At an initial weight of 280 pounds, R.C. will range from 1.4 to 1.5 for the same variation in target weights.

2. If patients who are less than 20 per cent overweight are eliminated from consideration, the complete range of variation for R.C. is from 1.3 to 5.5. A value higher than 5.5 can occur only in a patient who is less than 20 per cent overweight. As the degree of overweight increases, the possible height of R.C. becomes smaller. Thus patients who are more than 30 per cent overweight will have R.C. values no higher than 4.0 and patients who are more than 40 per cent overweight will have R.C. values below 3.0.

3. For a fixed initial weight, R.C. becomes larger as the target weight is larger. Thus, higher values of R.C. indicate that the amount of surplus weight is small, regardless of the patient's initial weight. Conversely, lower values of

R.C. will occur when the surplus weight is large or when the initial weight is high. Thus, an R.C. of 2.0 or less will occur almost exclusively in patients who weigh over 200 pounds.

These properties of the reduction coefficient illustrate how it can be used numerically to characterize the initial status of obese patients. A group of patients in a dietary program previously could be described in terms of the average and range values for their initial, surplus, target, and/or per cent excess weights. The individual (and mean) value of the reduction coefficient can perform this characterization more efficiently as a single datum since it contains components of all these variables.

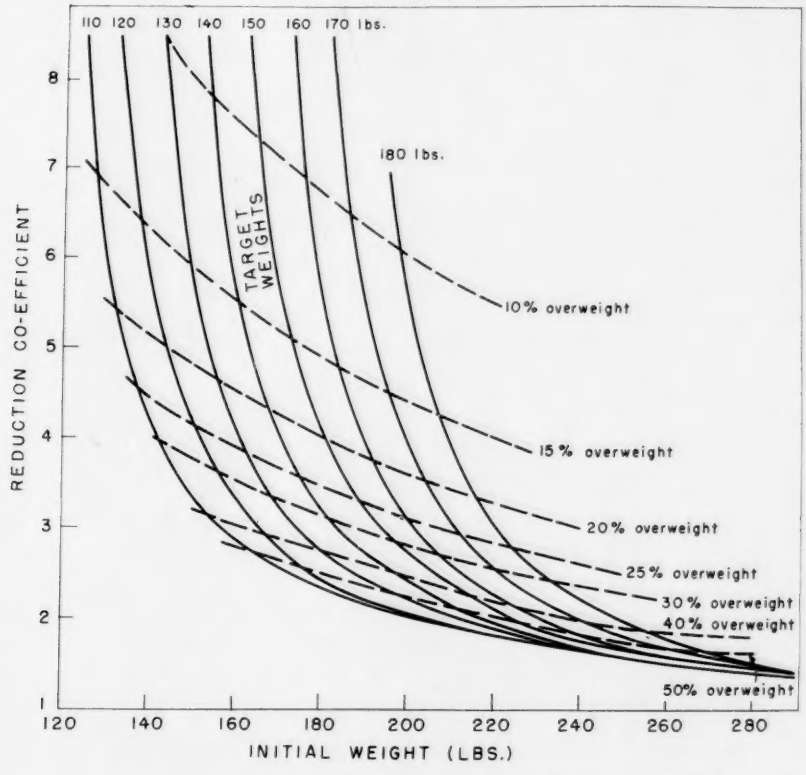

Fig. 1.—Variation of reduction coefficient with different initial weights as influenced by arbitrary choices in target weights. (When the patient's initial weight is known, the selection of the target weight will determine the percentage of overweight and the reduction coefficient, as shown on the graph.)

APPLICATION OF THE REDUCTION INDEX

Table II gives the interrelationships of the data obtained in 106 patients followed in an obesity clinic during a dietary study, the details of which have been reported elsewhere.[21] It lists details of the various parameters of dietary accomplishment in each patient and simultaneously shows the values of the reduction coefficient and reduction index. It will be noted that most of the

TABLE II. CLINICAL DATA AND COMPUTATION OF REDUCTION COEFFICIENT AND REDUCTION INDEX FOR 106 PATIENTS IN A DIETARY PROGRAM

PATIENT	W_I (POUNDS)	W_T (POUNDS)	$\frac{W_I}{W_T}$	W_S (POUNDS)	W_L (POUNDS)	D (DAYS)	RATE (GM./DAY)	PER CENT EXCESS WEIGHT LOST $\left(\frac{W_L}{W_S} \times 100\right)$	TRULSON PERFORMANCE	REDUCTION COEFFICIENT	REDUCTION INDEX
L. A.	218	177	1.23	41	43	57	343	105	S	3.00	129
N. B.	221	125	1.77	96	30	106	129	31	S	1.84	55
A. B.	267	157	1.70	110	10	27	169	9	U	1.55	15
R. B.	279	137	2.04	142	9	8	418	6	U	1.44	18
S. B.	189	122	1.55	67	20	71	128	30	S	2.31	46
J. C.	233	134	1.74	99	89	284	143	90	S	1.76	156
M. C.	235	151	1.56	84	1	37	12	1	U	1.85	2
I. C.	292	134	2.18	158	38	246	70	24	S	1.38	52
C. C.	212	128	1.66	84	49	260	86	58	S	1.97	97
D. C.	233	145	1.61	80	45	254	81	56	S	2.01	90
A. C.	172	119	1.45	53	42	174	110	79	S	2.73	115
J. C.	222	169	1.31	53	60	132	207	113	S	2.48	149
B. D.	256	131	1.96	125	18	83	99	14	U	1.57	28
C. D.	244	138	1.77	106	19	22	392	18	U	1.67	32
H. E.	203	139	1.46	64	7	41	78	11	U	2.28	16
A. F.	184	150*	1.23	34	31	72	196	91	S	3.61	112
C. F.	216	155	1.39	61	18	41	211	31	U	2.29	43
S. G.	267	169	1.58	98	77	216	162	79	S	1.61	124
R. G.	277	155	1.79	122	6	13	210	5	U	1.47	9
R. G.	292	131	2.23	161	34	113	137	21	U	1.39	47
D. G.	201	140	1.44	61	43	162	121	70	S	2.35	101
B. G.	320	150	2.13	170	9	4	1023	5	U	1.26	11
V. H.	204	135	1.51	69	23	76	138	33	U	2.19	50
E. H.	225	145	1.55	80	18	34	241	22	U	1.94	35
R. K.	380	133	2.86	247	109	328	151	44	S	1.16	126
R. K.	249	141	1.77	108	57	314	83	53	S	1.64	94
S. K.	223	149	1.50	74	17	20	387	23	U	2.02	34
E. K.	195	138	1.41	57	10	69	66	18	U	2.48	25
D. L.	225	130	1.73	95	26	106	112	27	S	1.82	47
J. L.	205	125	1.64	80	42	120	159	53	S	2.05	86
J. L.	256	186	1.38	70	34	278	56	49	U	1.97	67
N. M.	351	137	2.56	214	111	244	207	52	S	1.20	133
J. M.	210	151	1.39	59	20	50	182	34	U	2.36	47

VOL. 10 1959

H. M.	232	133	1.74	99	73	155	214	74	S	1.76	129		
A. M.	241	142	1.70	99	41	300	62	41	S	1.72	70		
F. N.	250	137	1.83	113	18	13	629	16	U	1.62	29		
R. P.	195	135	1.45	60	23	106	99	38	S	2.41	55		
K. P.	249	151	1.65	98	15	22	310	15	U	1.68	25		
M. R.	259	126	2.06	133	10	76	60	8	U	1.55	16		
P. R.	181	138	1.31	43	34	92	168	79	S	3.05	104		
J. R.	204	124	1.65	80	14	57	112	18	U	2.06	29		
S. S.	222	133	1.67	89	13	69	86	15	U	1.88	24		
M. S.	192	121	1.59	71	10	8	568	14	U	2.23	22		
C. W.	188	138	1.36	50	57	161	161	114	S	2.72	155		
B. W.	244	141	1.73	103	37	113	149	36	S	1.68	62		
C. W.	303	140	2.17	163	44	99	202	27	S	1.33	58		
H. W.	250	136	1.84	114	70	186	171	61	S	1.61	113		
R. F.	200	134	1.49	66	66	383	78	100	S	2.26	149		
E. R.	355	139	2.56	216	32	62	235	15	U	1.18	38		
P. A.	192	125	1.54	67	43	224	87	64	S	2.29	99		
B. A.	215	134	1.61	81	11	14	357	14	U	1.98	22		
C. A.	179	114	1.57	65	37	231	73	57	S	2.42	90		
A. B.	190	141	1.35	49	37	139	121	76	S	2.75	102		
B. B.	179	136	1.32	43	42	152	126	98	S	3.06	129		
L. B.	308	152	2.03	156	49	209	107	35	S	1.30	64		
C. B.	181	141	1.28	40	23	173	60	57	S	3.21	74		
S. B.	218	132	1.65	86	38	49	352	44	S	1.92	73		
F. C.	153	133*	1.15	20	20	35	260	100	S	5.76	115		
M. C.	207	138	1.50	69	25	175	65	36	S	2.17	54		
R. D.	157	129	1.22	28	26	139	85	93	S	4.35	113		
S. E.	198	137	1.45	61	13	34	174	21	U	2.37	31		
M. F.	236	125	1.89	111	26	48	246	23	U	1.70	44		
D. F.	261	200*	1.30	61	45	63	324	74	S	2.14	96		
S. F.	189	151	1.25	38	7	40	79	18	U	3.29	23		
J. F.	223	144	1.55	79	6	5	545	8	U	1.96	12		
R. F.	173	126	1.37	47	19	203	43	40	S	2.92	55		
D. F.	200	134	1.49	66	28	166	77	42	S	2.26	63		
A. G.	236	136	1.74	100	7	5	636	7	U	1.74	12		
Y. G.	245	142	1.73	103	35	61	261	34	S	1.68	59		
P. G.	225	134	1.68	91	15	152	45	17	U	1.84	28		
J. K.	147	127*	1.16	20	10	19	239	50	S	5.79	58		
G. K.	167	133	1.26	34	0	—	—	—	U	3.70	—		
B. K.	157	125*	1.26	32	0	—	—	—	U	3.93	—		
B. L.	167	116	1.44	51	0	—	—	—	U	2.82	—		

TABLE II. CLINICAL DATA AND COMPUTATION OF REDUCTION COEFFICIENT AND REDUCTION INDEX FOR 106 PATIENTS IN A DIETARY PROGRAM—Cont'd

PATIENT	W_I (POUNDS)	W_T (POUNDS)	$\frac{W_I}{W_T}$	W_S (POUNDS)	W_L (POUNDS)	D (DAYS)	RATE (GM./DAY)	PER CENT EXCESS WEIGHT LOST $\left(\frac{W_L}{W_S} \times 100\right)$	TRULSON PERFORMANCE	REDUCTION COEFFICIENT	REDUCTION INDEX
C. L.	197	122	1.62	75	32	217	67	43	S	2.15	69
H. L.	254	146	1.74	108	9	20	205	8	U	1.61	15
E. M.	232	135	1.72	97	59	203	132	61	S	1.77	104
E. M.	262	134	1.96	128	12	83	66	9	U	1.53	18
R. M.	231	139	1.66	92	46	78	268	50	S	1.81	83
E. M.	209	127	1.65	82	56	188	136	68	S	2.01	113
I. N.	175	129	1.36	46	12	21	260	26	U	2.95	35
R. P.	172	147	1.17	25	0	—	—	—	U	4.68	—
H. P.	264	151	1.75	113	0	—	—	—	U	1.55	—
V. P.	158	138*	1.15	20	20	42	216	100	S	5.72	115
P. R.	226	151	1.50	75	45	110	186	60	S	2.00	90
L. R.	206	147	1.40	59	34	116	133	58	S	2.38	81
N. R.	376	149	2.53	227	165	588	128	73	S	1.11	183
L. R.	212	145	1.46	67	7	48	66	10	U	2.18	15
A. S.	256	136	1.88	120	95	197	219	79	S	1.57	149
A. S.	242	144	1.68	98	16	65	112	16	U	1.72	27
R.S.	185	128	1.45	57	21	98	97	37	S	2.53	53
M. S.	198	148	1.34	50	54	127	193	108	S	2.67	145
V. S.	166	136	1.22	30	39	98	181	130	S	4.07	159
B. S.	196	147	1.33	49	14	40	159	29	U	2.72	38
S. S.	208	149	1.40	59	7	40	80	12	U	2.36	17
A. S.	175	142	1.23	33	25	62	183	76	S	3.74	93
S. T.	237	138	1.72	99	14	25	254	14	U	1.74	24
M. V.	195	150*	1.30	45	46	140	150	102	S	2.89	133
E. W.	280	144	1.95	136	46	159	132	34	S	1.43	66
I. W.	203	126	1.61	77	0	—	—	—	U	2.09	—
J. W.	186	130*	1.43	56	40	161	113	71	S	2.17	87
K. W.	205	152	1.35	53	0	—	—	—	U	2.54	—
S. W.	178	126	1.41	52	15	47	145	29	U	2.72	41
R. Z.	185	135	1.37	50	29	150	88	58	S	2.74	79
E. Z.	231	120*	1.93	111	111	236	214	100	S	1.74	193
S. Z.	160	138	1.16	22	10	62	73	45	U	5.27	53
Average	224	139	1.60	83.3	31.8	118	172	42.8	—	2.31	66

*Target weight selected arbitrarily. All other target weights chosen from standard weight tables.

patients were markedly overweight. The average weight of the group was 224 pounds with an average relative initial obesity (W_I/W_T) of 1.60. The average surplus weight was 83 pounds. All the target weights in this group were selected from the standard weight tables of the 1912 insurance survey,[6] with the exception of 8 patients. Six of these had target weights which were lower, and 2 had target weights which were higher than the corresponding standard weights. The "weight loss" (W_L) was taken as the lowest weight achieved during the active dieting. Column *D* represents the time elapsed from the beginning of the dieting to the date at which the lowest weight was achieved. The rate column represents the weight loss divided by the days in which this loss occurred, converted to grams per day. The per cent excess weight loss column was computed by dividing the weight loss by the surplus weight. The column marked "Trulson performance" indicates whether or not the patients were successful in accordance with the criteria of Trulson, Walsh, and Caso[12] described previously. The reduction coefficient and reduction index were computed as described in the text.

OL.
10
959

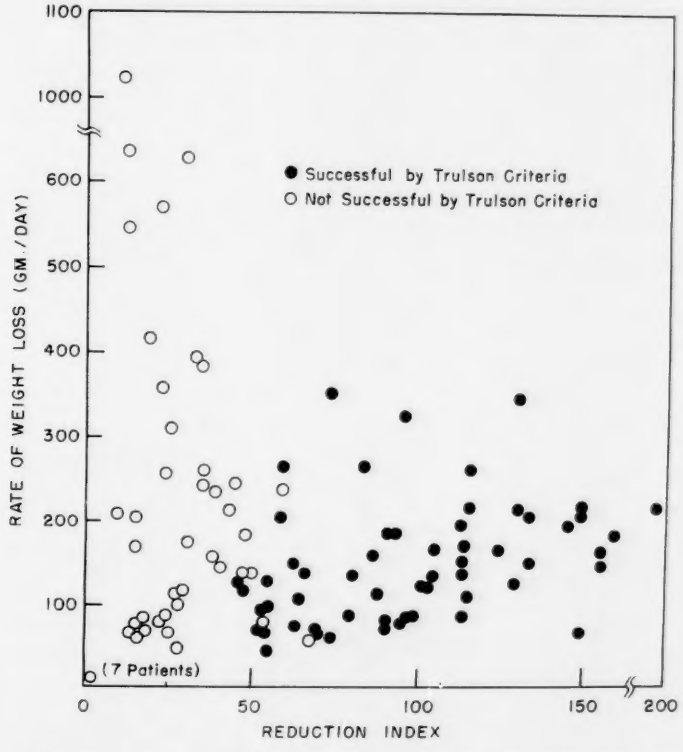

Fig. 2.—Relationship between rate of weight loss, success according to Trulson criteria, and reduction index for 106 patients in a dietary program.

Fig. 2 shows a simultaneous plot of the rate of weight loss compared with the reduction index and the Trulson performance for the patients in this group. The solid circles represent patients who were successful by the Trulson criteria

TABLE III. COMPARISONS OF DIFFERENT DIETARY PROGRAMS; RESULTS EXPRESSED WITH REDUCTION INDEX AND OTHER PARAMETERS

INVESTIGATOR	TREATMENT	GENERAL STATUS	TOTAL NUMBER STARTED	TOTAL NUMBER REPORTED	AVERAGE R.C.*	AVERAGE RATE (GM./DAY)	PER CENT SUCCESSFUL (TRULSON CRITERIA)	PER CENT WHO LOST AT LEAST 20 POUNDS	PER CENT WHO LOST AT LEAST 40 POUNDS	AVERAGE R.I.†	PER CENT WHO HAD R.I. AT LEAST 60
Controlled Environment											
Brown and Ohlson[23]	1,000-1,200 calorie high carbohydrate	Nutritional table	8	8	4.63	109	100	88	13	108	100
Leverton and Gram[24]	1,200 calorie high carbohydrate	Nutritional table	12	12	3.38	162	83	58	0	62	67
Young[25]	1,400 calorie high protein	Nutritional table	10	10	3.86	123	60	40	0	64	60
Young and associates[26]	1,400 calorie high protein	Nutritional table	6	6	4.48	122	83	50	0	79	83
Outpatients; Total Number Not Reported											
Jolliffe and Alpert[27]	1,000-1,500 calorie high protein	"Controls"	?	44	3.71	110	16	9	0	45	30
Jolliffe and Alpert[27]	1,000-1,500 calorie high protein	Performance index study	?	44	4.08	119	30	20	0	84	48
Lesses and Myerson[28]	1,400 calories Benzedrine	Private patients	?	8	2.53	95	75	75	25	67	75
Moritz[29]	Whole milk as sole source of food	Clinic	?	8	2.73	345	25	38	13	47	25
Pelner[30]	Benzedrine; ? specific diet	Thyroid also used	?	6	3.97	85	100	100	33	114	100

VOL. 10 1959

TABLE III. COMPARISONS OF DIFFERENT DIETARY PROGRAMS; RESULTS EXPRESSED WITH REDUCTION INDEX AND OTHER PARAMETERS—Cont'd

INVESTIGATOR	TREATMENT	GENERAL STATUS	TOTAL NUMBER STARTED	TOTAL NUMBER REPORTED	AVERAGE R.C.*	AVERAGE RATE (GM./DAY)	PER CENT SUCCESSFUL (TRULSON CRITERIA)	PER CENT WHO LOST AT LEAST 20 POUNDS	PER CENT WHO LOST AT LEAST 40 POUNDS	AVERAGE R.I.†	PER CENT WHO HAD R.I. AT LEAST 60
Outpatients; Totally Reported											
Feinstein and associates[21]	900 calorie formula diet	Special clinic	106	106	2.31	184	56	59	31	66	47
Hawirko and Sprague[31]	1,100 calories plus Dexedrine	Private patients	162	72	3.17	83	28	28	5	69	23
Jolliffe and Alpert[20]	1,000-1,500 calories; high protein	Special friends	11	11	5.64	157	73	55	0	96	91
Jolliffe and Alpert[20]	1,000-1,400 calorie plus citrus juice	Private patients	73	42	4.32	124	18	11	0	61	27

*Reduction coefficient.
†Reduction index.

and the open circles represent those who were unsuccessful. This figure shows graphically the inadequacy of the "rate" as a measurement of dietary accomplishment. It will be noted that the highest rates obtained in this group were in patients who were "unsuccessful" by the Trulson criteria and who had the lowest values for reduction index.

Fig. 2 also serves to relate "success" according to the Trulson criteria with achievement as measured by the "reduction index." It may be seen that all patients with reduction index values of 45 or lower were "not successful," that all patients with reduction index values of 70 or higher were "successful," and that in the intermediate range from 46-69, 15 patients were "successful" and 6 were "unsuccessful." Because of the arbitrary nature of the reduction index, its use would be simplified if patients were divided into a "successful" and an "unsuccessful" group using a single value as the border line. We have arbitrarily chosen a reduction index of 60 for this purpose and consider results of this value or higher to represent "success." With these standards, the particular dietary program used for illustration may be characterized as follows: 106 patients, with a mean reduction coefficient of 2.31 (range 1.11-5.79), achieved a mean reduction index of 66 (range 0-183). Forty-seven per cent achieved R.I. values of 60 or higher.

Table III shows how the R.C. and R.I. values may be used to compare different dietary reports. It gives the results of these indices for 13 weight reduction programs, the available data of which permitted the computation of these values. This table also gives the results of these programs using various other methods of expressing dietary accomplishment. The following points in this table are of particular interest:

1. The first four programs occurred in the controlled environment of "nutritional tables," a factor which significantly contributes to successful results.[22]

2. The next five programs do not cite the total number of outpatients who began the diet. It must be presumed that the published results report a selective group of successful patients rather than a representative sampling.

3. The four programs listed in the last section of the table are the only available reports in which the data allow the computation of all the desired measurements in an outpatient regimen where all of the starting patients are accounted for. The highest average R.I. value for this set was 96, in Jolliffe and Alpert's[20] group of 11 special friends. The average R.C. in these patients was 5.64, however, which indicates that most members of this group were originally less than 20 per cent overweight (as described earlier in the text). Since many of these patients were not significantly obese, the "success" achieved in this group is not strictly comparable to the performances in the other 3 series. The average R.C. value of 2.31 found in Feinstein and co-workers'[21] patients on a formula diet is the lowest of any reported in Table III. This suggests a greater degree of adiposity in their starting patients and may account for the high per cent of this group who lost more than 20 or 40 pounds. The average R.I. values were relatively similar for the three major reports in this set. However, 47 per cent of the group on formula diet achieved an R.I. of 60 or more as compared to 23 and 27 per cent in the two other series.

VOL
10
195

VOL.
10
959

DISCUSSION

Numerous diets and dietary adjuncts have been described for the treatment of obese patients. The results have often been published without rigorous evaluation of the quantitative aspects involved. One reason for this may be the lack of an existing standard index by which dietary accomplishment may be measured. The present paper has attempted to establish a quantitative index—based on numerical aspects of weight loss—which can be used to evaluate individual and group performances. It has pointed out the inadequacy of present-day methods by which dietary results have been expressed and has put special emphasis on the need for reporting the results of the dietary program in terms of all of the patients who began the program and not merely those who completed it. The use of the suggested index in reporting new dietary results will enable general comparisons which have not previously been possible.

It should be noted that measurement of dietary accomplishment by such a numerical index neglects many other aspects of weight reduction. It ignores the different psychological and physiologic phenomena which are involved in the initial motivation and in the side effects which can occur during dieting. It considers only the amount of weight lost during the active weight reduction period and not the long-term maintenance result. It does not determine whether or not the patient has been taught "sound" nutritional principles for use in or after the period of dieting. However, all of these variables are difficult to measure and some of them are merely value judgments. Since most diets give the results of only the active period of weight reduction and since most of them offer no way of objectively evaluating psychological phenomena, it seems acceptable to apply the quantitative index as indicated for the active weight reduction period.

SUMMARY

The inadequacies of existing methods for expressing the results of weight reduction programs have been discussed and a new *reduction index* has been derived. The index requires that a target weight be established for each patient at the beginning of every dietary regimen. The target weight may be chosen from standard tables, from "ideal weight" tables, or arbitrarily on the basis of the physician's judgment. The new index is obtained by multiplying the per cent of excess weight loss by the relative initial obesity. Its component terms are a product of two factors: (1) a reduction coefficient, which can be computed at the beginning of the dieting, and (2) the amount of weight lost during the active dieting. The value of the reduction coefficient will characterize the patient's initial obese status. The reduction index will characterize the accomplishment in weight reduction. Individual "success" is considered to have been achieved by patients who obtain a reduction index of 60 or higher. The total results of a dietary regimen may then be expressed by stating the percentage of the patients who obtained reduction indices of 60 or higher.

The data obtained in a group of 106 dieting patients have been expressed in terms of existing methods of documenting weight loss, and the use of the new reduction index in this group has been demonstrated. The results of a series

of different dietary programs have been compared using the reduction index and other parameters of measurement.

It is suggested that the *reduction index* be adopted as a standard for expressing the data of weight reduction regimens in order that valid comparison can be given to the results of different dietary programs.

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VOL
10
195

OL.
10
959

Announcements

RESEARCH GRANT AND FELLOWSHIP PROGRAM OF THE NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION, INC.

The program of the New York Tuberculosis and Health Association has been modified in recent years to enable it to meet effectively the changing problems relating to the control and eventual conquest of tuberculosis. The contributions to the annual Christmas Seal Campaign from the many citizens of the Bronx, Manhattan, and Richmond are being expended to combat tuberculosis, particularly in those areas where the disease continues to be a major health problem. The Association believes that this aim is served best by increasing its contributions to scientific investigation over and beyond those placed at the disposal of the National Tuberculosis Association, its parent organization. The Association recognizes that our understanding of tuberculosis may be increased either by direct investigations of the disease or by more distantly related research. Accordingly, support of research includes areas of potential as well as direct importance to tuberculosis.

The James Alexander Miller Fellowship.—The James Alexander Miller Fellowship, named in honor of the physician who was one of the organizers and the first president of the Association, is offered to a highly qualified investigator to enable him to pursue research work anywhere in the United States in a field of interest to the Association. The stipend is $7,000 to $10,000, depending on need and experience. Term of the fellowship is one year; holder may apply for a second year. Candidates for the Miller Fellowship may apply to the Association for a grant-in-aid of their research work; if granted this would be in addition to the basic stipend. A candidate of superior qualifications who does not receive the Miller Fellowship may be awarded another fellowship with a smaller stipend. Priority will be given to applicants in the New York City area.

American Trudeau Society Fellowships.—The New York Tuberculosis and Health Association contributes toward the support of fellowships for young physicians in training in the New York City area. These fellowships are awarded by the American Trudeau Society. Inquiries should be directed to the American Trudeau Society, 1790 Broadway, New York 19, N. Y.

Grants-in-Aid of Research.—These grants are available for the support of the work of established investigators. The research supported by these grants-in-aid should have a potential relationship to the problems of tuberculosis. It should be work of sound scientific merit by qualified investigators in medicine, sociology, epidemiology, or basic sciences. It should be carried on in an approved university, hospital, or other institution in the New York City area and application should be made in the name of the institution. An amount not exceeding 15 per cent of the grant will be contributed for overhead expenses incurred by the institution providing support to the principal investigator. Grants do not include salary for the principal investigator.

Applications.—Application forms for fellowships or grants-in-aid may be obtained from the New York Tuberculosis and Health Association, 260 Park Avenue South, New York 10, N. Y. The forms for the latter require a description of the plan and objectives of the investigations and of the qualifications of the investigators. Applications must be received prior to November 15 for fellowships beginning July 1 of the following year. Announcement of the awards will be made early in January following the receipt of the applications.

Applications for grants-in-aid are due at least 6 months prior to the contemplated date of starting the research project.

NEW YORK HEART ASSOCIATION SYMPOSIUM ON SALT AND WATER METABOLISM

Salt and water metabolism will be the subject of a 2-day symposium to be held by the New York Heart Association at the Hotel Biltmore on December 11-12. Alfred P. Fishman, M.D., chairman of the Association's Scientific Sessions Committee, is in charge of the program, and 23 speakers will take up all phases of the subject.

The morning session on the first day, under the chairmanship of Homer W. Smith, Sc.D., will consider the "Theory of Solutions." Richard J. Podolsky, Ph.D., will discuss the "Structure of Water and Electrolyte Solutions"; Irving M. Klotz, Ph.D., "Protein Solutions"; and Alexander Mauro, Ph.D., "Semipermeable Membranes."

Robert F. Pitts, M.D., of Cornell University, will be chairman of the afternoon session on that day, devoted to "Intrarenal Sites of Salt and Water Exchange." Topics to be covered will be "Osmotic Concentration and Dilution in the Mammalian Nephron" by Carl Gottschalk, M.D., "Reabsorption of Sodium and Chloride Ions by the Amphibian and Mammalian Nephron" by Gerhard Giebisch, M.D., "Ion Exchange Mechanisms in the Nephron" by Robert W. Berliner, M.D., and "Stop-Flow Studies on Ion and Water Reabsorption in the Nephron of the Dog" by Richard L. Malvin, Ph.D., and Walter S. Wilde, Ph.D.

An after-dinner address that evening will be given by George Wald, Ph.D., of Harvard University, on "Salt, Water and Vertebrate Metamorphosis."

The second day will open with a session on "Extrarenal Salt and Water Metabolism," presided over by John V. Taggart, M.D., of Columbia University. "Connective Tissue" will be the subject of a paper by Saul J. Farber, M.D., "Ion Transport in the Gut" by Alfred Gilman, Ph.D., the "Salt Gland of Marine Birds" by Knut Schmidt-Nielsen, Ph.D., "Ion Movements in the Eye" by V. Everett Kinsey, M.D., and "Electrolyte Excretion in Bile" by Henry O. Wheeler, Jr., M.D.

The closing session will be devoted to "Extrarenal Regulation of Salt and Water Exchange," with George Sayers, Ph.D., of Western Reserve University, as chairman. Gordon L. Farrell, M.D., will speak on "Glomerulotropin," Louis Welt, M.D., on "Volume Receptors," Wilbur A. Sawyer, M.D., on "Antidiuretic Hormone," James G. Hilton, M.D., on "Adrenocorticotrophic Action of Antidiuretic Hormone," and Fred C. Bartter, M.D., on "Aldosterone."

Application for registration should be made to A. P. Fishman, M.D., c/o New York Heart Association, 10 Columbus Circle, New York 19, N. Y. No fee is involved.

VOL. 10 195